Risk factors related to chronic pain after breast cancer surgery

– A prospective cohort study

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DEDICATION

This work is dedicated to my parents Karaj Singh and Mohinder Kaur for their endless love and support throughout the course of my postgraduate program.

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LIST OF ABBREVIATIONS

ALD	Axillary lymph node dissection
AV	Ana Velly
BPI	Brief Pain Inventory
β	Regression coefficients
CPBCS	Chronic pain after breast cancer surgery
CINHL	Cumulative Index to Nursing & Allied Health
95% CI	95% Confidence Interval
EMLA	Eutectic Mixture of Local Anesthetics
EMBASE	Excerpta Medica Database
HK	Harsimrat Kaur
GAD-7	Generalized anxiety disorder - 7
ICN	Intercostobrachial nerve
JGH	Jewish General Hospital
NRS	Numeric Rating Scale
OR	Odds Ratio
PHQ-8	Physical Health Questionnaire - 8
p	P- value (calculated probability)
RCT	Randomized Control Trial
RR	Relative risk
r	Correlation coefficient
SD	Standard Deviation
SE	Standard Error
SR	Systematic Review
SLB	Sentinel lymph node biopsy
SM	Shrisha Mohit
Yrs	Years

ABSTRACT

Aim: Chronic pain after breast cancer surgery (CPBCS) is a significant clinical problem affecting 13% to 93% of patients. Furthermore, 5% to 10% of CPBCS patients are estimated to suffer from severe and disabling CPBCS. Thus, the aim of this prospective cohort study was to identify pre-, intra- and post-operative factors related to CPBCS risk and intensity at three months follow up.

Methods: Ninety-five female patients scheduled to undergo breast cancer surgery were recruited from the Jewish General Hospital, Montreal, Quebec. Baseline data was collected on age, pre-operative pain, anxiety, and depression. Telephone follow-up interviews were conducted at seven days and three months after surgery to assess the acute pain and CPBCS, respectively, using the brief pain inventory scale. Intra-operative data on type of surgery, axillary status, radiotherapy and chemotherapy was assessed from physicians' charts. Multivariable logistic regression and linear regression analyses were used to assess factors for CPBCS risk and CPBCS intensity, respectively, at three months follow-up.

Results: Eighty-two patients completed the three months follow-up. From those, 45 (55%) reported CPBCS, and 24 patients (53.33%) reported moderate pain (NRS 3–7). In the multivariable analyses only pre-operative pain (odds ratio (OR) = 4.41, $p = 0.03$) increased the CPBCS risk at three months after surgery. CPBCS intensity at three months after surgery was positively related to depression ($\beta = 1.55$; $p = 0.0005$), and chemotherapy ($\beta = 1.34$; $p = 0.006$).

Conclusion: Our results demonstrate that pre-operative pain increases the risk of CPBCS. Depression and chemotherapy were associated with CPBCS intensity. These factors should therefore be considered important to be evaluated and managed for the breast cancer surgery patient, in order to reduce the burden of CPBCS.

RÉSUMÉ

Objectif: La douleur chronique suivant la chirurgie pour le cancer du sein (CPBCS) et un problème clinique important, affectant de 13% à 93% des patients. De plus, on estime que 5% à 10% des patients atteints de CPBCS souffrent de CPBCS sévère et invalidant. Ainsi, le but de cette étude de cohorte prospective était d'identifier les facteurs pré-, intra-, et postopératoires, liés au risque et à l'intensité de CPBCS lors d'un suivi de trois mois.

Méthodes: Quatre-vingt-quinze patientes prévues pour la chirurgie pour le cancer du sein ont été recrutées à l'Hôpital général juif. Les données de bases sur l'âge, la douleur préopératoire, l'anxiété, et la dépression, ont été recueillies. Des entrevues de suivi ont été menées par téléphone à sept jours et trois mois après la chirurgie afin de déterminer la douleur aiguë et le CPBCS respectivement, en utilisant le « brief pain inventory scale ». Des données intra-opératoires sur le type de chirurgie, le statut axillaire, la radiothérapie et la chimiothérapie ont été recueillies à partir des fiches médicales des médecins. Des analyses de régression logistique multivariées et régression linéaire ont été utilisées afin d'évaluer les facteurs du risque et de l'intensité de CPBCS respectivement, lors d'un suivi de trois mois.

Résultats: À l'entrevue de suivi de trois mois, 45 (55%) des patientes présentaient le CPBCS, desquelles 24 patientes (53.33%) ont rapporté une douleur modérée (NRS 3-7) et une patiente (2.22%) avait de la douleur sévère (NRS>7) dans la région du sein. La douleur préopératoire (odds ratio (OR) = 4.41, $p = 0.03$) resta associée au CPBCS lorsque le modèle fut ajusté pour tenir compte des facteurs pré-, intra-, et postopératoires. La dépression ($\beta = 1.55$; $p = 0.0005$) et la chimiothérapie ($\beta = 1.34$; $p = 0.006$) contribuèrent à l'intensité de CPBCS trois mois après la chirurgie.

Conclusion: Nos résultats démontrent que la douleur préopératoire augmente le risque de CPBCS. La dépression et la chimiothérapie étaient associées à l'intensité du CPBCS. Ces facteurs doivent donc être considérés importants à évaluer et gérer auprès du patient prévu pour la chirurgie pour le cancer du sein, afin de diminuer le fardeau du risque et de l'intensité du CPBCS.

PREFACE

This thesis has followed a manuscript based thesis style. As per McGill University standards, the manuscripts included in thesis should be logically-coherent and should have a unified theme. The manuscripts in this thesis discuss a novel project on the risk factors related to chronic 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 pain after breast cancer surgery. Chapter three proposes the objectives of study based on knowledge provided by the literature. Following a comprehensive discussion of the methodology in chapter four, manuscripts are presented. Finally the last chapter discusses the methodological considerations and conclusion of the study.

Multiple authors have contributed in this thesis work; explicit appreciation of each author's contribution is mentioned in the following section.

CONTRIBUTION OF AUTHORS

Manuscripts:

1) **Risk factors related to chronic pain after breast cancer surgery: A systematic review**

2) **Risk factors related to chronic pain after breast cancer surgery: A 3-month prospective cohort study**

Harsimrat Kaur, Master's Candidate: Recruited patients for the study, carried out the statistical analysis and wrote the manuscripts.

Shrisha Mohit, Research assistant, Jewish General Hospital, Montreal, Quebec, Canada: Carried out the recruitment for the study and also revised the manuscripts 5.1 and 5.2.

Mervyn Gornitsky, Professor Emeritus McGill University & Director of Research Dental Dept. Jewish General Hospital, Montreal, Quebec, Canada: Contributed to design study and revised the manuscripts 5.1 and 5.2.

Richard Hovey, Associate Professor, Faculty of Dentistry, McGill University, Montreal, Quebec, Canada: Contributed to design study and revised the manuscripts 5.1 and 5.2.

Ana Miriam Velly, Associate Professor, Faculty of Dentistry, McGill University, Epidemiologist, Dental Dept. Jewish General Hospital, Montreal, Quebec, Canada: Conceived this investigation, designed and supervised this study, carried out statistical analysis, and contributed to manuscript writing.

1. INTRODUCTION

Breast cancer is the most frequent type of cancer among women and represents 12% of all new cancer cases in women.[1] Chronic pain is a significant clinical problem after breast cancer surgery (CPBCS). Even though advancements in surgical techniques have rendered surgical procedures less invasive in order to prevent CPBCS,[2] its prevalence remains very high (ranging from 13% to 93%).[3] Furthermore, 5% to 10% of CPBCS cases are estimated to suffer from severe and disabling CPBCS[4,5] diminishing the patient's health-related quality of life.[6]

The etiology of CPBCS is not well understood.[7,8] A number of putative risk factors for the development of CPBCS have been suggested, such as pain before[9] and early after surgery,[10-13] psychological factors,[14-17] type of breast cancer surgery,[18-21] adjunctive radiotherapy,[12,13,17] adjunctive chemotherapy,[17,22] and age.[5,6,10] However, due to several methodological limitations found in the available literature, it remains unclear which factors contribute to CPBCS. For example a large number of studies were conducted retrospectively and lacked a clear description of the study population and outcome, which may potentially decrease the internal validity of the studies. A literature review[4] conducted in 2011 emphasized the need to conduct a prospective cohort study to identify the risk factors related to CPBCS.

In a response to this gap in research, the primary aim of this study was to identify pre-operative (age, pre-operative pain, anxiety, and depression), intra-operative (type of surgery and axillary status) and post-operative (acute postoperative pain, radiotherapy and chemotherapy) factors that contribute to CPBCS onset three months following surgery. Our secondary aim was to determine if these pre-, intra- and post-operative factors were also related to CPBCS intensity three months after surgery. Intensity of chronic pain is relevant as it limits the abilities and activities of the patients to engage in their day-to-day life. To our knowledge only one other prospective cohort study[22] has assessed the risk factors related to CPBCS intensity.

2. LITERATURE REVIEW

2.1 Chronic pain after breast cancer surgery

The prevalence of chronic pain after breast cancer surgery (CPBCS) ranges from 13% to 93% in women with breast cancer who undergo surgery.[3] Moreover, 5% to 10% of women suffer from chronic, disabling CPBCS (score >5 out of a maximum score of 10).[23] CPBCS often persists for many years in patients. It has been shown by the study[24] that greater than 50% of patients report pain even at a mean 9 years of post-operative follow-up. Thus, CPBCS constitutes a significant clinical problem and has a strong impact on patients' quality of life.[25] Several types of chronic post-surgical pain have been described after breast cancer surgery: scar pain or chest wall pain (11-57%), arm and shoulder pain (12-51%), and phantom breast pain (13-24%).[7,8]

2.2 Prevalence of Chronic pain after breast cancer surgery

Prevalence of CPBCS is summarized in table 2-1. Point prevalence is measured at a single point in time for each patient. Period prevalence is the proportion of a population that has the condition at some time during a given period. It includes people who already have the condition at the start of the study period as well as those who acquire it during that period.[26]

CPBCS prevalence ranges from 8% to 82%.[15,18,19,27-30] Variability in the estimates were due to differences in CPBCS definition, study designs, surgical techniques, analgesic strategies, and adjunctive therapies used. For example, prevalence of CPBCS was 8.2% in a retrospective cohort study[31] (n = 196) that considered only severe post operative pain (NRS $\geq$ 5), 12 months after surgery. On the contrary, a prospective cohort study (n = 114)[22] that included all degrees of pain intensity (NRS = 1–10) showed a prevalence of 48.8%, 3 months after surgery.

Table 2-1: Prevalence of CPBCS and study characteristics							
Author	**Design**	**Sample**	**Instrument used**	**Groups**	**Analyzed**	**Prevalence CPBCS**	**Time of assessment**
Tasmuth *et al.*[32] 1995	RC	467	VAS; MPQ-F	Ma	283	32%[BS]; 41%[IA]	32m
				BC	184	45%[BS]; 61% [IA]	28m
Stevens *et al.*[33] 1995	CS	95	MPQ; CPQ; NRS	-	95	20%	-
Tasmuth *et al.*[34] 1996	PC	105	VAS	-	93	24%[BS] 17%[IA- 12m]	1Dbs; 1,6,12 m
Tasmuth *et al.*[12] 1997	RC	509	NRS	S_1	417	39%	10-54m
				S_2	92	24% [BR]	12 m
Carpenter *et al.*[35,36] 1998	RC	178	BPI	-	134	27%NP	37.6 m*
Salmon *et al.*[37] 1998	RCT	128	Di; CE	ICN+	66	4.5%	3, 6, 12, 18 m
				ICN -	62	1.6%	
Abdullah *et al.*[38] 1998	RCT	120	NR	ICN+	40	16%	3m
				ICN -	80	24%	
Maycock *et al.*[39] 1998	RC	150	3 point scale	SLB	39		3 y[#]
				ICN+	37	43%	
				ICN-	34	44%	
Smith *et al.*[40]1999	RC	511	Paindrawing; PSPQ	-	408	43%	6 y
Tasmuth *et al.*[13] 1999	RC	265	VAS; MPQ-F	LVU	92	56%	1 y
				HVU	129	43%	
Hack *et al.*[41] 1999	CS	248	MPOPQ; MPQ	-	222	72%[IA]; 31.1%[Ax]	33.2 m*
Fassoulaki *et al.*[42] 2000	RCT	46	VAS	EMLA	22	43%	0-6d; 3m
				Co	23	91%	
Johansen *et al.*[43] 2000	RC	266	4 point scale; CE	-	266	8%; 15%on CE	6.6y[#]
Gottrup *et al.*[44] 2000	CC	26	VAS; MPQ-D	CP	15	-	-
				Co	11		
Kuehn *et al.*[45] 2000	RC	396	5pointscale; CE	-	396	23%	34m*
Schrenk *et al.*[46] 2000	PC	70	VAS ; CE	ALD	35;	37.1%	17m
				SLB	35	5.7%	15.4m
Ververs *et al.*[47] 2001	RC	465	4 point scale; CE	-	400	21%	4.7 y*
Fassoulaki *et al.*[28] 2001	RCT	100	VAS	R+M	22	59%	0-24h; 2-6 d; 3 m
				R+P	24	71%	
				P+M	25	68%;	
				P+P	23	61%	
Ernst *et al.*[48] 2002	RC	148	VAS; CE	-	148	26	6-12m ;5y

Fassoulaki *et al.*[49]2002	RCT	75	VAS; VNS	M+P	21	45%	0,3,6,9,24 h, 3m
				G+P	22	54%	
				P+P	24	58%	
Swenson *et al.*[50] 2002	PC	261	5 point scale	ALD	78	46.8%	1,6, 12 m
				SLB	169	28.7%[12m]	
Haid *et al.*[51] 2002	RC	235	3point scale; CE	ALD	140	47%	25m
				SLB	57	19.3%	18m
Caffo *et al.*[52] 2003	RC	757	MPQ-I	BC	348	39.7% CP	12m
				Ma+ IBR	75		
				Ma	145		
Amichetti *et al.*[53] 2003	RC	481	MPQ-I	-	324	43.5%	39 m[#]
Peintinger *et al.*[54] 2003	PC	56	MPQ-G; VAS;CE	ALD	31	25.9%	BS; 7d; 9-12 m
				SLB	25	24.8%	
Torresan *et al.*[55] 2003	RCT	87	Ques; NE	ICN+	42	NR	2d, 40d, 3m
				ICN-	43		
Schijven *et al.*[56] 2003	RC	393	4 point Likert scale	ALD	213	23%	3m- 3y
				SLB	180	7.8%	
Veronesi et al.[21] 2003	RCT	200	-	ALD	100	91%	6m and 24m
				SLB	100	16% [6m]	
Freeman[57] 2003	RCT	120	-	ICN-	39	32%	3y
				ICN+	34	15%	
Taylor[58] 2004	RC	208	3pointscale	ICN+	48	45.3%	2.5-6 y
				ICN-	53		
				ICNU	69		
Reitman[59,60] 2006	PC	204	VAS	-	189[1y] 181[2y]	-	BeS; 1 ,2y
Leidenius[61] 2005	RC	274	4 point Scale	ALD	47	30%	3y
				SLB	92	12%[AP]	
Barranger[62] 2005	PC	115	3 point Scale	ALD	51	52.9%	20.3m
				SLB	54	21.2%	
				SLB-AL	10	60%	
Karki *et al.*[63] 2005	RC	110	VAS	-	96	26%[6m] 22.9%[12m]	6, 12m
Fassoulaki *et al.*[64] 2005	RCT	50	VAS	MA+G	22	45%	3, 6, 9h; 1-8d;3,6m
				Co	22	82%[3m]	
Macdonald *et al.*[6] 2005	RC	138	MPQ; UCSF	-	113	52% [9y]	9 y*
Gulluoglu *et al.*[65] 2006	RC	85	BPI-T; VAS	-	85	46%	6m
Kairaluoma *et al.*[18] 2006	RCT	60	VAS; POMS	PV	29	8.3% NP	1, 6 and 12 m
				Co	30		
Poleshuck *et al.*[22] 2006	PC	114	NRS	-	95	48.8%[3m]	BS; 2, 10 d; 1,3 m
Schulze *et al.*[66]	RC	134	SAQ	SLB	19	15.8%	31.4m

2006				SLB-ALD	56	67.9%	56.4 m
Passavanti *et al.*[67] 2006	AC	300	MPQ;VAS; NT	-	128	43%	6, 7, 9, 11, 14m
Iohom[68] 2006	RCT	29	VAS; MPQ	Std anal (I)	15	80%	1, 2, 3, 4, 5d, 10w
				PV (II)	14	0	
Ishiyama *et al*[69] 2006	CS	247	1-5 scale	-	193	73%	3.8 y[#]
Kudel *et al.*[20] 2007	RC	504	VAS	-	278	54.7%	20.4 m*
Langer *et al.*[70] 2007	PC	449	Di	SLB	441	8.1%	31 m[#]
				SLB-ALD	210	21.1%	29.5m[#]
Eisenberg et al[71] 2007	RCT	22	NuPS; MPQ	Ama	9	79%[3m]; 100%[6m]	1,3 ,6m
				Co	8	80%[3m]; 78%[6m]	
Steegers *et al.*[72] 2008	RC	495	VAS	-	317	32%	23m[#]
Vilholm *et al.*[5] 2008	RC	1032	NRS	BC	219	23.9%	18m
				Re	563		
Vilholm *et al.*[73] 2008	RCT;CO	27	NRS	-	25	NR	-
Bianco *et al.*[74] 2008	RCT	374	4-point scale	ALD	341	18%	6m;12m; 18m;24m
				SLB	331	10%[6m]	
Gartner *et al.*[75] 2009	CS	3754	NRS	-	3253	47%	26m
Peuckmann *et al.*[25] 2009	RC	1783	SAQ	-	1316	29%	5 y
Fecho *et al.*[31] 2009	RC	196	NRS	-	196	8.2%	1m; 6-12m
Amr *et al.*[76] 2010	RCT	150	VAS	VG	50	26%	4,12, 24h; 2-10d; 6m
				GG	50	64%	
				Co	50		
Jud *et al.*[77] 2010	CS	343	VPM	-	343	-	-
Rief *et al.*[14] 2011	L	3088	SI (0-3)	-	2160	-	4 y
Fabro *et al.*[29] 2012	PC	203	Psychologis-t handbook	-	174	52.9%	45days PO; 6 m
Elkaradawy *et al.*[19] 2012	RCT	50	VAS; NPS	MA	21	39%[bs]; 72.1%[IA]	24h; 1,3, 6 and 9 m
				Co	22		
Jain *et al.*[78] 2012	RCT	86	BPI;MPQ; VNS	De	34	8.8%[gp]; 32.3%[rp]	72 h; 3m
				Co	35	60%[gp], 22.8%[rp]	
Sheridan *et al.*[79] 2012	CS	111	LANSS;CPAQ; VAS	-	111	29.7%	64.5 m[#]

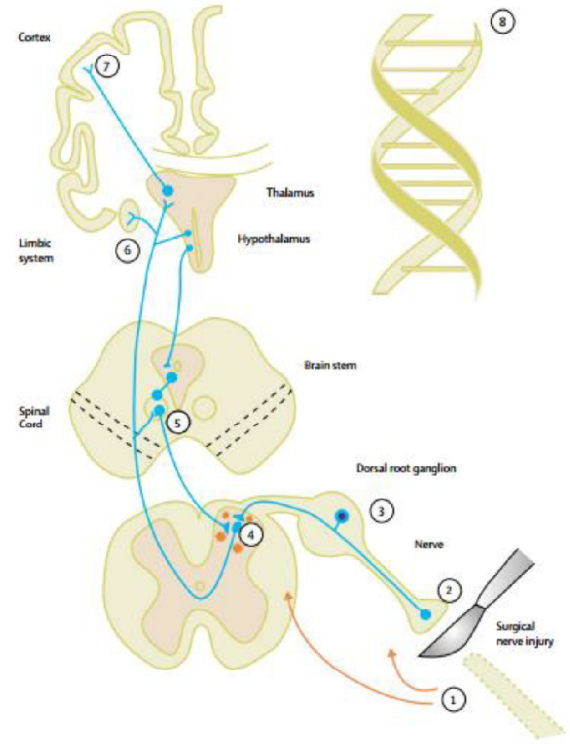
Sipila *et al.*[9] 2012	PC	553	NRS	-	489	56%MP 12.9%M-SP	BeS; 6 m
Bokhari F.N. *et al.*[80]2012	PC	17	BPI;Pain charts	-	17	24%	2d, 10 d and 3 m
Mohamed S A *et al.*[81]2013	RCT	140	VAS; DN4	Co	35	34.29%	2-48hr;1 and 2 m
				BG	35	14.29%	
				C1G	35	17.14%	
				C2G	35	14.3%	
Albi-Feldzer*et al.*[82] 2013	RCT	236	VAS;BPI; DN4	RV	111	33%	6-24h;3, 6,12 m
				Co	108	27%[3m]	
Belfer*et al.*[15] 2013	CS	1097	BPI;MPQ; BCPQ		495	32.5%	3.2 y
Cho *et al.*[83]2013	CS	228	NRS	Pr	86	44.2%	2.5-4 y
				Se	89	67.4%	
Kaunisto *et al.*[84] 2013	PC	1000	NRS	-	1000	Under study	5 y
Mejdahl *et al.*[85] 2013	RCS	2828	NRS	-	2411	45%[2y] 37%[6y]	2 and 6 y
Schreiber *et al.*[16] 2013	CC	200	BCPQ;BPI; MPQ	Ca	102	-	6m
				Co	98		
Sun *et al.*[86]2013	RCT	60	NRS	Group F	30	33%[6m]; 10%[12m]	2-48h; 2,4,6, 12m
				Co	30		
Wilson *et al.*[87] 2013	RC	470	physician Diagnoses	-	470	14.7% NP	12 m
Bell *et al.*[88]	PC	1683	NR	-	1205	44.8%[3m]	1-5year
Bruce *et al.*[10] 2014	PC	362	BPI; DN4; LANSS	-	308[4m] 293[9m]	68%[4m] 63%[9m]	PO; 1 w; 4, 9 m
Chiu *et al.*[27] 2014	RCT	132	NRS; BPI	TPVB	58	8%	12 m
				LA	60		
De Oliveira *et al.*[30] 2014	PC	300	BPI; MPQ	-	300	37%	6 m
Karmakar *et al.*[89] 2014	RCT	180	VRS	GA	60	73%[3m]	Po; 3, 6 m
				GA+ TPVB	57		
				GA+ CTPB	60		
Stephens *et al.*[11] 2014	PC	516	PPQ; BSQ; NRS	-	410	11.6% SP	2wks,1- 6 m
Miaskowski *et al.*[90] *2014*	PC	410	ASQ;NRS; PPQ	-	398	23.6%MP 34.8%MoP[AP]	1, 2, 3, 4, 5, 6 m
Bredal *et al.*[17] 2014	CS	1332	NRS; BPI	-	832	41%CP; 33.8%NP	2-6 y
Meretoja *et al.*[91] 2014	PC	970	NRS	-	860	50%MP; 16%M-SP	12 m
Terkawi *et al.*[92]2015	RCT	71	NRS	Li	34	12%	6m
				Co	27	30%	
Shahbazi *et*	CC	122	NRS; SAQ	Ca	61	-	-

***al.*[93]2015**				Co	61		

ASQ, Arm/ Shoulder Symptoms Questionnaire; Ama, amatadine; Ax, axilla; AP, arm pain; ALD, axillary lymph node dissection; BeS ,before surgery; BS, breast surgery; BC, breast conservative surgery; BCPQ, Breast Cancer Pain Questionnaire; BSQ, breast symptomatic questionnaire; BR, breast region; BG, bupivacaine group; BPI, brief pain inventory; BPI-T, brief pain inventory Turkish version; CE, clinical examination; CPAQ, Chronic Pain Acceptance Questionnaire; CPQ, Cancer Pain Questionnaire; CC, case control; CP, chronic pain; CS, cross-sectional; CTPVB, continous thoracic paravertebral Block; CC, case control; Ca, cases; Co, control; C1G, clonidine 150+bupivacaine;C2G,clonidine250+bupivacaine;Di,dichotomous;DN4,DouleurNeuropathique4;De,dexmedetomidine;Dbs ,daybeforesurgery;EMLA,eutecticmixtureof local anesthetics; GG, Gabapantingroup;G+P,gabapantin+placebo; GP, generalized pain; GA, general anesthesia; Group F, flurbiprofen axetil; HVU, high volume unit; ICN(+), intercostobrachial nerve preserved; ICN(-), intercostobrachial nerve sacrificed;ICNU, intercostobrachial nerve status unknown; IBR,immediate breast reconstruction; IA, ipsilateral arm; L, longitudinal study; LA, local anaesthesia; LANSS; self-Administered Leeds Assessment of Neuropathic Symptoms and Signs;LVU, low volume unit; Ma, mastectomy; MA, multimodal analgesia; MA+G, multimodal analgesia + gabapentin; MP, mild pain; MoP, moderate pain; m, month; MPOPO,Modified Post-operative Pain Questionnaire; MPQ, McGill pain questionnaire; MPQ-F, McGill pain questionnaire finnish; MPQ-G, McGill pain questionnaire german; MPQ-D, McGill pain questionnaire dannish; MPQ-I, Mcgill pain questionnaire Italian; M-SP, moderate- severe pain; NP, neuropathic pain; NPS, neuropathic pain scale; NE, neurologic examination; NuPS, numeric pain scale; NR, not reported; NT, neurometer test; NRS, numeric rating scale; PC, prospective cohort; PV, paravertebral block; PSPQ, pain service patient questionnaire; PPQ, post surgical pain questionnaire; PO, pre-operative; Po, post-operative; Pr, propofol; P+M, placebo+ mexiletine; P+P, placebo + placebo; R+M, regional block +mexiletine; R+P, regional block + placebo; Re, reference group; RC, retrospective cohort; R, reported; RP, regional pain; RCS, repeated cross-sectional study; RCT, randomized control trial; RCT-CO, randomized control trial cross over design; RV, ropivacaine; SI, symptom inventory; S1, sample 1; S2, sample 2; SP, severe pain; Se, Sevoflurane; SAQ, self administered questionnaire; SLB, sentinel lymph node biopsy; SLB-ALD, sentinel lymph node biopsy followed by axillary lymph dissection; TPVB, thoracic paravertebral block; VNS, verbal numeric score; VAS, visual analog scale; VPM, visual pain mapping; VG, Venlafaxine; wks, weeks; *, mean;#, median

2.3 Etiology of CPBCS

The etiology of CPBCS is not well understood.[7,8] Peripheral and central neuronal sensitisation contribute to postoperative chronic pain.[8] Acute pain may arise from damage to peripheral tissue and nerves, as with breast cancer surgery (figure 2-1) leading to increased spontaneous firing and alterations in the transduction, conduction or neurochemical sensitivity of nociceptive afferent fibers.[94] There are cascade of events which involves enhanced ion channel permeability, gene expression, and receptor and channel density on the cell membrane leads to peripheral nociceptor hyperexcitability, termed 'peripheral sensitization'. Persistence of peripheral sensitization contributes to excitation of the dorsal horn or higher centers in the central nervous system, thus contributing to central sensitization (figure 2-2).[95] Cytokines, chemokines, and neuropeptides are implicated in the pathophysiology of the peripheral and central sensitization.[94]



1) Denervated Schwann cells and infiltrating macrophages distal to nerve injury produce local and systemic chemicals that drive pain signalling.
2) Neuroma at site of injury is source of ectopic spontaneous excitability in sensory fibres.
3) Changes in gene expression in dorsal root ganglion alter excitability, responsiveness, transmission, and survival of sensory neurons.
4) Dorsal horn is site of altered activity and gene expression, producing central sensitisation, loss of inhibitory interneurons, and microglial activation, which together amplify sensory flow.
5) Brainstem descending controls modulate transmission in spinal cord.
6) Limbic system and hypothalamus contribute to altered mood, behaviour, and autonomic reflexes.
7) Sensation of pain generated in cortex (past experiences, cultural inputs, and expectations converge to determine what patient feels).
8) Genomic DNA predispose (or not) patient to chronic pain and affect their reaction to treatment.

Figure 2-1: Sites and mechanisms responsible for chronic postsurgical pain. Reprinted with permission from Elsevier publisher; article by Kehlet H, *et al*. "Persistent postsurgical pain: risk factors and prevention," from The Lancelet, Vol. 367,pages 1618-25.

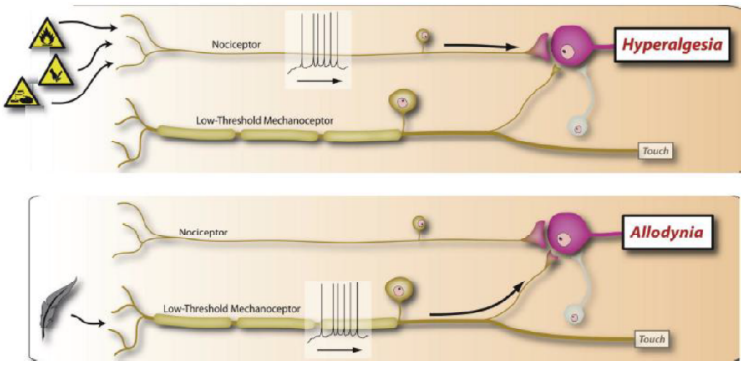


Figure 2-2: Effects of central sensitization. Reprinted with permission from Wolters Kluwer Health, Inc.; article by Clifford J. Woolf "Central sensitization: Implications for the diagnosis and treatment of pain," from PAIN, 152 (2011), pages S2–S1

2.4 Putative risk factors for chronic pain after breast cancer surgery

A risk factor always precedes the onset of disease (outcome). Multiple putative risk factors have been implicated in the development of CPBCS, such as genetics, age, comorbidities, psychological factors, type of breast surgery, axillary status, intercostobrachial nerve, perioperative pain management, acute pain, adjunctive therapies and post-operative complications. In this section, several studies with an overview of risk factors of CPBCS are discussed.

2.4.1 Genetics

Only one prospective cohort study[11] investigated the association between genetic makeup and CPBCS at 6 month after surgery using multivariable analyses. They showed that patients with interleukin [IL] 1 receptor 2 rs11674595 were at higher risk (OR= 36.1) to develop CPBCS (p = 0.015) than those without this receptor. In addition, patients with IL10 haplotype[11] were less likely to have CPBCS by 79% (p = 0.037) (Table 2-2).

2.4.2 Age

A positive relationship between young age (< 55 yrs) and CPBCS was found in 42.22% (19/45) of studies.[5,6,17,22,29,30,32,40,50,52,65,72,75,80,83,85,88,90,96] The magnitude of the OR ranged from 2.01 to 5.23 (Table 2-2). Out of these 19 studies, eight were prospective cohort, eight retrospective cohort and three cross-sectional studies (Table 2-2). A prospective cohort studies with follow-up at 3 months,[22,80] and at $\geq$ 6 months,[29,30,50,88,90,96] showed that young patients had an increased risk to develop CPBCS regardless of other risk factors. Similarly, retrospective cohort studies with $\geq$ 6 months[5,6,32,40,52,65,72,85] of surgery, showed young age to be related to CPBCS. It was interesting that one prospective cohort study[9] found older age ($\geq$ 70) to be associated with CPBCS at 6 months after surgery using the Bayesian analyses.

2.4.3 Psychological factors

Four out of 10 studies identified that anxiety[14-17] contributes to CPBCS. Out of these, one was a 4 – year longitudinal study,[14] two cross-sectional,[15,17] and one case-control study[16] (Table 2-2). The magnitude of the OR was weak ranging from 1.12 - 1.83.

Four studies – 4 year longitudinal study,[14] 1 year retrospective cohort study,[13] cross-sectional[17] and case-control study[16] – demonstrated that depression was related to CPBCS regardless of other risk factors. The magnitude of the OR for depression ranged from 1.10 - 2.07.

Two studies[15,16] assessed catastrophizing as a risk factor for CPBCS. A case-control[16] showed that patients with catastrophizing were almost four times as likely to have CPBCS (OR = 3.46) as compared to a non-catastrophizing control group. A cross-sectional study[15] found a moderate correlation between catastrophizing (r = 0.43) and CPBCS after 3.2 years of surgery.

These previous results, however, are not consistent with three prospective cohort studies with a large sample size (>110).[22,90,91] The multivariable logistic regression analyses showed that patients exposed to higher level of anxiety and depression were not more likely to develop CPBCS than patients without anxiety or depression at 3[22] and 12 months[91] of surgery ($OR_{anxiety}$ = 1.03; p = 0.97) (Table 2-2).

2.4.4 Comorbidities

A positive relationship between comorbidities and CPBCS was found in 73% (11/15)[9,11,17,20,22,30,35,36,47,79,87,88,90,91,97] of studies, with the magnitude of the OR ranging from 2.53[17] to 8.71,[11] where analyses were adjusted for other risk factors (Table 2-2). More specifically, pre-operative pain (OR = 2.90; $p < 0.001$),[9] diabetes mellitus (OR = 2.61; p = 0.002),[98] diabetic neuropathy (OR = 8.17; $p < 0.0001$),[98] and fibromyalgia (OR = 2.64; p = 0.03)[98] were associated with an increased risk of CPBCS after 6[9] and 9[98] months of surgery. Out of these 11 studies, six were prospective,[9-11,14,90,91] three retrospective,[20,47,87] and two cross-sectional[17,79] studies (Table 2-2).

However, 3 months[22] and 6 months[11,30] prospective cohorts including 95 to 410 women with breast cancer did not find that preoperative breast pain (OR = 0.84; p = 0.76), pain in other part of body (p = 0.54), and diabetes (p = 0.079) contribute to CPBCS, regardless of other risk factors. In addition, a prospective cohort study[9] suggested that the CPBCS risk was modified by pre-operative pain intensity. Women with more severe pre-operative pain (>4; NRS 0-10) had

increased risk (OR = 2.90; $p < 0.01$) to develop CPBCS, in comparison to those without pre-operative pain after 6 months of follow-up.

2.4.5 Type of surgery

From thirty-three studies that have evaluated the impact of different types of surgery on CPBCS, only three studies found a positive relation between CPBCS and type of surgery. Out of these, two retrospective cohort studies at 12 months[12] and 32 months after surgery[32], showed breast-conserving surgery to be related to CPBCS (OR= 1.68) regardless of other risk factors. On the contrary, one cross-sectional study[77] showed by pictogram that patients with mastectomy had an additional field of pain over the chest wall in comparison to those who underwent breast-conserving surgery.

2.4.6 Axillary lymph node dissection (ALD)

A positive ALD contribution was identified in the majority of the studies (80%) that evaluated ALD as a factor for the development of CPBCS, when compared to sentinel lymph node biopsy (SLB). From those 24 positive studies, two were RCTs,[21,74] 19 cohort studies[29,30,43,46,48,50,51,54,56,59-62,66,70,72,90,91,96] and three cross-sectional studies. In these studies, CPBCS was defined at different duration of follow-up: 3,[56] 6[29,30,90] and >6 months.[43,46,48,50,51,54,59-62,66,70,72,91,96] The magnitude of effect found in these studies ranged from 1.22 to 7.7 (Table 2-2 and 2-3).

2.4.7 Intercostobrachial nerve (ICN)

Four RCTs[37,38,55,57] and four cohort[10,39,58,87] studies assessed the role of preservation of ICN (Table 2-2 and 2-3). From those, one 3 months RCT[55] and one retrospective cohort study,[58] where data was collected between 2.5 and 6 years of surgery, showed that ICN incision was associated with CPBCS in comparison to ICN preservation (Table 2-2 and 2-3). However, three RCTs at 3 months,[38] 18 months,[39] and 3 year of follow-up,[37,38,57]and three cohort studies[39,96,98] at 9 months of follow-up with adequate sample size($n > 100$) found non-significant results. Furthermore, one retrospective cohort study[39] ($n = 150$) did not find any increased risk of development of CPBCS but CPBCS intensity was much more likely to be moderate or severe (3 point scale) in the nerve-divided group ($p< 0.0001$) (Table 2-2).

2.4.8 Perioperative pain management

Eighteen studies evaluated the effect of perioperative strategies on CPBCS prevention. In a parallel RCT,[42] EMLA decreased the incidence of CPBCS at 3 months after surgery. Another parallel RCT comparing Venlafaxine[76] and gabapentin showed that incidence of CPBCS was less at 6 months in the Venlafaxine group (26%) as compared to the gabapentin group (64%) (Table 2-3). Intravenous flurbiprofen axetil was effective in decreasing CPBCS in comparison to placebo ($p < 0.05$) at 12 months of follow-up.[86] The use of perioperative lidocaine[92] infusion was also found to be associated with a decreased risk of CPBCS at 6 months after surgery (OR = 0.05; $p = 0.034$) (Table 2-3). Perioperative infusion of dexmedetomidine reduced the pain scores and the analgesic requirement during the first 72 h of observation and CPBCS at 3 months compared to control group ($p < 0.01$).[78] A parallel RCT[64] showed that EMLA and gabapentin have a positive effect on CPBCS at 3 months after surgery, decreasing the risk of CPBCS ($p = 0.028$).

Preincisional paravertebral block was shown to significantly decrease the risk of CPBCS at 2 ($p = 0.009$),[68] 6 ($p = 0.029$) and 12 months ($p = 0.003$)[18] follow-up when compared to the control group in a parallel RCT. On the other hand, a RCT (n = 180; $p = 0.13$)[89] did not find any significant difference in the incidence of CPBCS at 6 months between the thoracic paravertebral block and placebo groups after breast-conserving surgery. Another RCT showed propofol to be effective in reducing CPBCS as compared to sevoflurane (OR = 2.55; $p = 0$ .007).[83]

Negative results are listed in Table 2-3. Two RCTs (n = 75; n = 100)[28,49] showed that regional block, mexiletine and gabapentin have no effect on CPBCS risk at 3 months of follow-up. In a RCT cross-over trial (n = 25), Levetiracetam did not decrease the incidence of neuropathic CPBCS ($p = 0.83$).[73] A parallel RCT,[82] including 236 patients allocated to local wound infiltration with either ropivacaine or saline, did not find a positive effect on CPBCS at 3 months follow-up. A RCT[19] that used bupivacaine found that it did not have any effect on CPBCS[19] as compared to the control group at 9 months after surgery ($p = 0.66$) (Table 2-3).

2.4.9 Acute postoperative pain

Nine studies assessed the effect of acute postoperative pain in the development of CPBCS (Table 2-2), out of which six found a positive relationship. The risk identified by the prospective studies ranged between 1.34 and 2.02.[10,11] Furthermore, this risk appears to be higher among individuals with a more severe acute postoperative pain (NRS >6) (Table 2-2). Patients exposed to moderate to severe acute postoperative pain present an increased risk of CPBCS (NRS $\geq$5) compared to those with mild acute postoperative pain.[10] In addition, severity of acute postoperative pain also contributed to moderate to severe chronic pain at 4 and 9 months[10] after surgery where the model was adjusted for other risk factors (Table 2-2).

2.4.10 Radiotherapy

One third[12,13,17,25,32,47,65,69,72,75,91,92] of 36 studies showed that radiotherapy is associated with CPBCS (Table 2-2). A prospective cohort analysis of an RCT[92] demonstrated in multivariate analyses that patients undergoing radiotherapy had a significantly higher risk of CPBCS (OR= 28.62; p = 0.008) at 6 months after surgery. On the contrary, another prospective cohort study,[30] including 300 participants, found that radiotherapy was associated with the development of CPBCS at 6 months after surgery, in the univariate model (p = 0.04). However this significant effect did not remain in the multivariable model (OR = 1.05; p =0.85) adjusted for age, axillary lymph node dissection and basal metabolic rate.

It is suggested that the risk between radiotherapy and CPBCS is modified by the dosage of radiotherapy. A retrospective cohort study[43] (n = 266) did not find an increased risk of CPBCS when they used radiation dosage of <50 Gy, after 6.6 years (median) of surgery. Two other retrospective cohort studies, where additional boost doses of radiotherapy were used, showed increased CPBCS risk at 12 months of surgery.[12,13]

2.4.11 Chemotherapy

Nine (25%)[17,32,41,72,79,88,90,91,98] of 36 studies suggested chemotherapy as risk factor for the development of CPBCS. Patients who underwent chemotherapy were two to three times as likely to develop CPBCS compared to patients without chemotherapy regardless of other risk factors (Table 2-2).[79,91]

The majority of studies,[12,13,30,31,45,47,50,52,56,59,60,77,91,92] however did not find an association between chemotherapy and CPBCS. Among those studies that described the drugs used for chemotherapy, two cross-sectional studies[83,85] demonstrated that chemotherapy with cyclophosphamide,[85] epirubicin,[85] fluorouracil[85] or paclitaxel[83] were not associated with CPBCS.

2.4.12 Hormonal therapy

Twenty one studies assessed endocrine therapy as a potential risk factor, and only one 4-year longitudinal study[14] showed that tamoxifen treatment increased the risk of CPBCS (p= 0.001) (Table 2-2).

2.4.13 Postoperative complications

Only two studies out of 10 confirmed the positive association of CPBCS and post-operative complications. In a retrospective cohort study (n = 467),[32] postoperative bleeding predicted CPBCS in the breast scar area at 32 months after surgery(Table 2-2). A cohort study[29] including 174 patients showed that women having tissue necrosis had 40% less chance of developing CPBCS (Relative Risk, RR = 0.60). A prospective cohort[88] (n=1205) found that patients with lymphedema (p = 0.002) were more likely to have CPBCS as compared to patients without lymphedema, where analyses were adjusted by age, chemotherapy and extent of tumor. Another prospective cohort study[29] showed that lymphedema (RR = 1.54) and the presence of axillary web syndrome (RR = 1.70) increase the CPBCS risk at 6 months follow-up.[29] This risk, however, did not persist when the analyses were adjusted for age and axillary lymph node dissection.

Table 2-2: Risk factors assessed related to CPBCS in observational studies							
Author	**Demo**	**Physochological**	**Comorbidity**	**Surgery**	**Adjunctive treatment**	**Acute pain**	**Complications**
Tasmuth *et al.*[32] 1995	**Age***	-	-	**ST (BC>Ma)***	**RTX,*CTX** * HTX	POP	Bleeding, Seroma*
Tasmuth *et al.*[34] 1996	-	-	-	ST	-	-	-
Tasmuth *et al.*[12] 1997	Age	-	**Pain** (OR=1.57^{BS} OR=1.65^{IA})	**ST (BC>Ma)*** (OR=1.7^{BS} OR=1.7^{IA}), LNR,TFS, T size	**RTX*** (OR=2.2^{BS} OR=2.3^{IA}) CTX, HTX	**POP*** (OR=1.57^{BS} OR =1.65^{IA})	Comp
Carpenter *et al.*[35,36] 1998	Age, Race, MS,Income ,Edu,Emplo -yment	-	Physical comorb	ST	RTX, CTX, HTX	-	-
Maycock *et al.*[39]1998	-	-	-	**ICBN**[#]	-	-	-
Smith *et al.*[40]1999	**Age,*** Edu, BMI	-	-	-	-	-	-
Tasmuth *et al.*[13] 1999	Age	Anx, **Dep***(OR= 1.10)	-	T stage, ST, LNR	**RTX*** (OR=4.68), CTX, HTX	**POP*** (OR= 1.65)	Bleeding, Seroma, Infection
Hack *et al.*[41] 1999	**Age**[#]	-	-	TFS, **LNR**[#], Number of positive nodes	RTX, **CTX**[#]	-	-
Johansen *et al.*[43] 2000	Age, Menopausal status	-	-	**ALD***	RTX, CTX, HTX	-	-
Gottrup *et al.*[44] 2000	-	-	-	Sensory testing	-	-	-
Kuehn *et al.*[45] 2000	Demograph	-	-	Time interval, Number of	CTX	-	-

	-ic			involved nodes, ES			
Schrenk *et al.*[46] 2000	-	-	-	**AxP (ALD)***	-	-	-
Ververs *et al.*[47] 2001	Age,MS, Edu, Insurance	-	**Comorb*** (OR= 3.38)	ST	RTX, CTX, HTX	-	-
Ernst *et al.*[48] 2002	-	-	-	ST, **AxP (ALD)***	-	-	-
Swenson *et al.*[50] 2002	**Age,*** BMI	-	-	ST, **AxP (ALD)***	CTX	-	-
Haid *et al.*[51] 2002		-	-	**AxP (ALD)***	-	-	-
Caffo *et al.*[52] 2003	**Age***	-	-	ST, LNR	CTX	-	-
Peintinger *et al.*[54] 2003	-	-	-	**AxP (ALD)***	-	-	-
Schijven *et al.*[56] 2003	Age	-	-	ST, **AxP (ALD** OR = 3.23),* T stage, TFS	RTX, CTX, HTX	-	-
Taylor[58] 2004	-	-	-	**ICBN***	-	-	-
Reitman[59,60] 2006	-	-	-	**AxP (ALD)***[2y]	-	-	-
Leidenius[61] 2005	-	-	-	**AxP (ALD)**[IA]***	-	-	-
Barranger[62] 2005	-	-	-	**AxP (ALD)**[IA]***	-	-	-
Karki *et al.*[63] 2005	-	-	-	**BC > Ma**[AxP] **BC >Ma** [BS]	-	-	-
Macdonald *et al.*[6] 2005	**Age,*** **BMI***	-	-	TFS	-	-	-
Gulluoglu*et al.*[65] 2006	**Age***	-	-	ST	**RTX,***CTX, HTX	-	Comp
Poleshuck*et al.*[22] 2006	**Age*** (OR= 0.95), Race, Edu,	Anx, Dep	Preop	**ST**[#] (β = 0.24), T stage, Prior breast cancer	**RTX**[#] (β= 0.31) CTX	**Severe POP**[#] (β = 0.28)	-

	MS						
Schulze *et al.*[66] 2006	-	-	-	**AxP (ALD)***	-	-	-
Passavanti *et al.*[67] 2006	-	-	-	**Ma+BR>Ma*** [#] 6m Ma+BR>MRM 14m	-	-	-
Ishiyama et al[69] 2006	Age	-	-	ST, TFS, T stage	**RTX*** (OR=3.3), CTX	-	-
Kudel *et al.*[20] 2007	Age, Edu, MS, Race	-	**Preop***	TFS, LNR, BR	RTX, CTX, HTX		-
Langer *et al.*[70] 2007	-	-	-	**AxP* (SLB** OR = 0.33)* [IA]	-	-	-
Steegers*et al.*[72] 2008	**Age***	-	-	ST, **AxP (ALD)***	**RTX,* CTX***	-	Comp
Vilholm*et al.*[5] 2008	Age (OR = 1.04), smoking	-	-	ST, AxP, **T location*** (OR = 6.48), **Previous operations*** (OR= 8.12)	RTX, CTX	-	-
Gartner *et al.* [75] 2009	**Age*** (OR = 3.62)	-	-	ST, **AxP*** (**ALD*** OR= 1.77)	**RTX*** (OR=1.50), CTX	-	-
Peuckmann *et al.*[25] 2009	**Age***(OR = 0.48),BMI, Edu***(less edu**,OR= 1.55),status *(**single**,OR = 1.81)	-	-	ST, TFS	**RTX*** (OR =1.43)	-	-

Fecho*et al*.[31] 2009	Age,**Race*** (**non white**), Insurance, Obesity	-	Comorb	-	RTX, CTX	-	-
Jud *et al*.[77] 2010	-	-	-	T size, Nodal status, ST* (**Ma>BC**)	RTX, CTX, HTX	-	-
Rief*et al*.[14] 2011	Age, **Edu*** (**higher education)**	**Dep,*Behavior variables,*** Exercise	**Baseline pain score***		**HTX*** (**tamoxifen**)		
Fabro*et al*.[29] 2012	**Age*** (RR = 5.23), BMI, Employment, Edu	-	-	ST, **AxP*** (**ALD,** RR= 2.01)	RTX, CTX, HTX	-	Comp
Sheridan *et al*.[79] 2012	Age	-	**Preop*** (OR= 5.17)	ST, TFS	RTX, **CTX*** (OR=3), HTX	-	-
Sipila *et al.*[9] 2012	**Age*** (OR=2.01), **BMI*** (OR=3.38), Alcohol, **Smoking*** (OR =2.41)	-	**Preop*** (OR=2.90), **CP*** (OR= 2.99)	**Previous operations*** (>4; OR= 2.91), ST, AxP, T stage	RTX, CTX, Preop use of HTX	-	Comp
Bokhari F.N. *et al*[80].2012	**Age,*** Gender, BMI	-	Preop	ST, **More invasive surgery***	-	**POP***	-
Belfer*et al.*[15] 2013	Age, Other demog, Exercise, **Sleep*** (β= 0.13)	**Anx*** (β= 0.26), Dep (β=-.14), **Catastrophizing** *(β=.47), **Somatization*** (β=2.78), Stress, Emotional	-	ST, AxP, BR	RTX, CTX	-	Comp

		stability					
Cho *et al*[83]2013	Age (OR = 0.95)	-	-	Surgery duration, **AxP*(ALD** RR = 1.59)	RTX, HTX, **Sevoflurane** *(RR=1.51)	-	-
Mejdahl et al[85] 2013	**Age*** (OR =1.78)	-	-	ST, **AxP*(ALD** OR = 2.04)	RTX, CTX	-	-
Schreiber et al.[16] 2013	Age, BMI, Reoccuranc -e	**Catastrophizing (OR=3.46),* Dep(OR=1.39)* Anx(OR=1.12)*,** stress	-	AxP, ST,BR	RTX, CTX, HTX	-	Comp
Wilson et al[87] 2013	Age, **Race** (**AA** OR=1.78) *	-	DM (OR=1.98), FM (OR= 2.75)	ST, AxP, ICBN	RTX, **CTX*** (OR= 2.85)	-	
Bell et al[88]	**Age,*** Edu,	-	-	ST, **Beyond stage 1* (**OR = 1.66)	RTX, **CTX*** (OR =1.74), HTX	-	**Lymph edema***
Bruce, et al[10] 2014	Age* (OR=0.91), BMI	**Optimism** (OR= 0.70)*	Preop	ST, AxP (**ALD**, OR= 2.97),[9m] ICBN	RTX, CTX, HTX	**POP*** (OR=1.34)[4m] (OR=1.17)[9m]	-
De Oliveira *et al*[30] 2014	**Age*** (OR=0.98), Height, Weight	-	Comorb	ST, Surgical duration, **AxP*** (**ALD** OR= 7.7), T stage, BR	RTX, CTX	-	-
Stephens, *et al*[11] 2014	**Genetics*** (IL1R2 OR = 36.07), IL10 (OR= 0.2),	-	Comorb, **Preop*** (OR= 8.71)	-	-	**Severe POP*** (OR =2.02)	-

	Age,Edu, Employment,MS,BMI, Exercise						
Miaskowski,*et al*[90] *2014*	**Age,*** **Ethnicity*** (non white), Edu, MS, Income	Dep, Anx	**Preop***	ST, **AxP*** (**ALD)**	**CTX,*** RTX	-	-
Bredal et al[17] 2014	**Age*** (OR=3.52), Edu, MS	**Anx***(OR=1.83), **Dep***(OR =2.07)	**Comorb*** (OR =2.53)	ST**,** **AxP*** (**ALD)** (OR=1.68)	**RTX*** (OR=1.69), **CTX*** (OR =1.87), HTX	-	-
Meretoja *et al*. [91] 2014	BMI	Dep, Anx,	**Preop*** (OR =0.70)	Previous operations, T size, LNR, AxP (**SLD*** OR= 0.40)	**RTX*** (OR=0.51), **CTX*** (OR = 1.47) HTX	-	-
Shahbazi*et al.*[93]2015	Age, BMI	-	-	-	-	-	-

*, Significant risk factor for CPBCS; # ,Significant factor for intensity of CPBCS; Anx, anxiety; AA, African American; ALD,axillary lymph node dissection; AxP, axillary procedure; BC, breast conservative surgery; BS, breast scar; BR, breast reconstruction; CPBCS, chronic pain after breast cancer surgery; CC, case control; CP, chronic pain; CS, cross-sectional; Comp, complications; Comorb, comorbidities; CTX, chemotherapy; DM, diabetes mellitus; dep, depression; edu, education;ES, extend of surgery; FM, fibromyalgia; HTX, hormonal therapy; IA, ipsilateral arm; IBR,immediate breast reconstruction; L, longitudinal study; LNR, lymph nodes removed; MS, marital status; Ma, mastectomy; m, month; PC, prospective cohort ; PO, pre-operative; Po, post-operative; POP, post operative pain; preop, preoperative pain; QST, quantitative sensory testing; RCS, repeated cross-sectional study; RC, retrospective cohort; RTX, radiotherapy; SLB, sentinel lymph node biopsy; ST, surgery type; T location, tumour located in the upper lateral quarter;T size, tumor size; TFS, time from surgery; UA, unadjusted; wks, weeks; *, mean;#, median

Table 2-3: Risk factors assessed related to CPBCS in Randomized Controlled Trials	
Author	**Risk factors assessed**
Salmon *et al.*[37] 1998	ICBN
Abdullah *et al.*[38] 1998	ICBN
Fassoulaki *et al.*[42] 2000	**EMLA***
Fassoulaki *et al.*[28] 2001	Regional block, oral mexiletine, and the combination of both
Fassoulaki *et al.*[49]2002	Gabapentin with an increased dose of mexiletine
Torresan *et al.*[55] 2003	**ICBN***
Veronesi et al.[21] 2003	AxP* (**ALD**)[6m,24m]
Freeman[57] 2003	ICBN
Fassoulaki *et al.*[64] 2005	**MMA+G***
Kairaluoma *et al.*[18] 2006	**PVB***[12m]
Iohom[68] 2006	**PVB***
Eisenberg *et al*[71] 2007	Amantadine
Vilholm *et al.*[73] 2008	Effect of Levetiracetam
Bianco *et al.*[74] 2008	AxP* [**SLB**(OR .52)][6m]
Amr *et al.*[76] 2010	Venlafaxine and gabapantin* (**GG>VG**)
Elkaradawy *et al.*[19] 2012	Multimodal analgesia
Jain *et al.*[78] 2012	**Dexmedetomidine***
Mohamed S A *et al.*[81]2013	Clonidine + topical bupivacaine
Albi-Feldzer *et al.*[82] 2013	Age, BMI, anx, dep, ST, RTX,CTX,HTX, Ropivacaine
Sun *et al*[86] 2013	i.v.**flurbiprofen axetil**[2*, 4*, 6*, 12m]
Chiu *et al*[27] 2014	TPVB and LA
Karmakar *et al*[89] 2014	TPVB - GA (RR= 1); GA+TPVB (RR= .83); GA+CTPVB (RR= .80)
Terkawi *et al.*[92]2015	**Li*** (OR .05),age, BMI, ST, AxP, **breast implant***(OR 16.19),CTX,**RTX*** (OR 28.62), HTX
BG, bupivacaine group; CTPVB, continous thoracic paravertebral Block; Ca, cases; Co, control; C1G, clonidine 150 + bupivacaine; C2G, clonidine250+bupivacaine; De,dexmedetomidine;Dbs,daybeforesurgery; EMLA,eutectic mixture of local anesthetics; GG, Gabapantingroup; G+P,gabapantin+placebo; GP, generalized pain; GA, general anesthesia; Group F, flurbiprofen axetil; ICN(+), intercostobrachial nerve preserved; ICN(-), intercostobrachial nerve sacrificed; ICNU, intercostobrachial nerve status unknown; LA, local anaesthesia;; MA, multimodal analgesia; MA+G, multimodal analgesia + gabapentin; PV, paravertebral block; Pr, propofol; P+M, placebo+ mexiletine; P+P, placebo + placebo; R+M, regional block +mexiletine; R+P, regional block + placebo; Re, reference group; RP, regional pain; RV, ropivacaine; SP, severe pain; Se, Sevoflurane; SLB, sentinel lymph node biopsy; SLB-ALD, sentinel lymph node biopsy followed by axillary lymph dissection; TPVB, thoracic paravertebral block; VG, Venlafaxine	

3. STUDY OBJECTIVES

The overall objective of this study was to identify factors associated with CPBCS at three months follow-up.

More specifically, our aim was:

I. To determine whether preoperative risk factors (age, preoperative pain, anxiety, and depression) increase the risk related to CPBCS at 3 months of follow-up.

   Hypothesis 3.1: Age, preoperative pain, anxiety, and depression didn't increase the risk of CPBCS at 3 months of follow-up.

II. To determine whether intraoperative risk factors (type of surgery and axillary status) increase the risk related to CPBCS at 3 months of follow-up.

   Hypothesis 3.2: Type of surgery and axillary status didn't increase the risk of CPBCS at 3 months of follow-up.

III. To determine whether postoperative factors (acute postoperative pain, radiotherapy and chemotherapy) increase the risk of CPBCS at 3 months of follow-up.

   Hypothesis 3.3: Acute postoperative pain, radiotherapy and chemotherapy didn't increase the risk of CPBCS at 3 months of follow-up.

   Our secondary aim was to assess if these pre-, intra- and post-operative risk factors contribute to CPBCS intensity.

4. METHODOLOGY

In this chapter ethics, study design, study population, data collection and statistical analyses used to assess the study objectives of the manuscript will be explained in detail.

4.1. Ethics

The protocol of the study was approved by the research ethics committee of the JGH prior to the start of the study. The surgeons (Drs. Sigman, Boileau, and Basik)/nurses pre-screened the patients to participate and quickly presented the study to the patients. If the patients showed interest, they were asked to agree verbally to be contacted by Harsimrat Kaur (HK) and Shrisha Mohit (SM). HK contacted the patients to discuss all aspects of the study and obtained their informed consent.

4.2. Study design

A cohort analysis was used in this study. Cohort study is a type of observational epidemiologic study in which the investigator selects a group of exposed and unexposed individuals and follows them over time for development of the outcome of the interest. Rothman[99] defined it as "Any designated group of individuals who are followed or traced over a period of time." There are three types of cohort studies: 1) prospective, 2) retrospective and 3) ambiseptive. These differ only with respect to timing of data collection. In this study we collected the data prospectively that has low risk of bias in exposure measurement since the outcome status is not known. This design has many advantages 1) it provide evidence for temporality between exposure and disease, 2) it allow to study multiple outcomes simultaneously, 3) useful in studying rare exposures, 4) useful for studying disease incidence, and 4) allows for direct calculation of risk ratios and risk differences.

But this study design has few limitations 1) it is hard to maintain study participants over time, 2) it is inefficient for studying rare diseases, and 3) can be costly/time consuming. Furthermore, this design has various biases that will be explained in detail in the discussion chapter.

4.3. Study population

For this cohort study, female breast cancer patients were recruited from the list of patients from the Segal Cancer Center at the JGH. This hospital was selected because its associated Segal Cancer Center treats a significant population of breast cancer patients in Montreal. The participants were recruited between November, 2014 and September, 2015.

4.3.1. Inclusion and Exclusion criteria

Women 18 years of age or older, who were incident cases with breast cancer and who were scheduled to undergo breast cancer surgery, were invited to participate in this study. The exclusion criteria was: (i) Patients who did not undergo surgery; (ii) Previous cancer of any kind; (iii) Karnofsky performance status under score 50, which includes patients who will require considerable assistance and frequent medical care; (iv) metastasis; (v) No access to a telephone; (vi) Pregnant women; and (vii) Males with breast cancer. With this eligibility, our study encompassed a large population that was at risk for CPBCS.

4.4. Assessment and data collection

4.4.1. Primary outcome - CPBCS

Chronic pain has traditionally been defined as pain that persists past the normal time of healing. For research purposes, three to six months have been used and are the most common and convenient point of division between acute and chronic pain.[100] In this manuscript, we defined CPBCS as pain present at 3 months after breast cancer surgery. This decision is supported by a statement by Kehlet *et al*. explaining that it is vital to select a conservative time frame of 3 months after the surgical procedure to have clinically relevant results.[101]

4.4.2. Secondary outcome

The secondary outcomes was: Average pain intensity measured by the BPI at 3 months after surgery.[102] Average pain was defined as the average of the responses to three different questions from BPI (each scale is presented as a row of equidistant numbers where 0 = “no pain” and 10= “worst pain possible”): “worst pain”, “average pain” and “pain now” ratings.

4.4.3. Data collection

The putative risk factor data was collected before surgery, on the day of surgery, and seven days after surgery. The study outcomes, primary and secondary, were assessed three months after surgery. Data before and after surgery were collected by HK and SM. This procedure has been used in prior studies.[103-106]

4.4.3.1. Before surgery: Preoperative breast pain, and psychological factors assessment

After recruitment, HK contacted the patients to schedule a time for the first interview before their surgery. Table 4-1 describes the questionnaires that were used in this interview.

Table 4-1: Questionnaires administered before surgery	
Domain	Measures
Informed Consent	-
Age	Questionnaire
Preoperative pain	BPI
Generalized Anxiety	GAD-7
Depression	PHQ-8

Preoperative pain. To assess preoperative breast pain, patients were invited to answer "Do you have pain or discomfort in your breast" (APPENDIX).

Anxiety, and depression. GAD-7 and PHQ-8 (APPENDIX) were used to assess anxiety, and depression respectively. Their validity and internal consistency are high.[107-111]

Age. HK or SM also asked the patients regarding their age.

4.4.3.2. On the day of surgery: surgical data assessment

Surgical data was collected from the patients' chart using ChartMaxx by HK.

4.4.3.2. Seven days after surgery: acute pain

Acute pain. At seven days after surgery, HK or SM called the participants to assess if they have any pain after surgery (APPENDIX). The questionnaires used in this interview are in Table 4-2.

Table 4-2: Questionnaires administered at 7 day after surgery	
Domain	Measures
Pain intensity	BPI

4.4.3.4. Three months after surgery

At 1 week before three months after participants' surgery, HK called the participants to remind them of their phone interview at three months after surgery. Table 4-3 describes the questionnaires that were used in this interview.

CPBCS. At this phone interview, HK or SM asked patients: "Do you have pain in your breast, arm or axilla?" Also, they were asked other three questions from the BPI to assess the pain intensity.[102] These questionnaires have excellent sensitivity, specificity and reliability.[102,112,113]

Table 4-3: Questionnaires administered at three months after surgery	
Domain	Measures
CPBCS, pain intensity	BPI

4.5. Statistical analysis

All analyses tested a null hypothesis of no statistical relationship between the independent and dependent variables of interest at α=0.05 significance. Chi- square and Fisher exact test was used to compare the distribution of the categorical variables. To assess the means of the continuous variables, Student's t- test was used. We assessed the risk factors for the onset of CPBCS three months following surgery using a multivariable unconditional logistic regression analyses (proc logistic, SAS). Odds ratios (ORs) and their 95% confidence intervals (CI) were estimated. Crude and multivariable linear regression analyses (proc mixed, SAS) were employed to determine the contributors to CPBCS intensity three months following surgery. Regression coefficient (β) and their 95% confidence intervals (CI) were estimated.

The primary outcome (dependent variable), whether or not an individual had CPBCS at three month following their surgery, is binary. The secondary outcome CPBCS intensity was continuous. Thus, risk factors associated with CPBCS were assessed with logistic regression and secondary outcome by linear regression analyses. Logistic regression equation can be written as:

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \sum_{i=1}^{k} \beta_i * X_i$$

Where,

P is the probability of Y =1 (the probability of the outcome)

X_i is the ith predictor variable, i = 1, 2, 3…k;

β_o is the log odds of probability of outcome when predictor variables have a value of zero

β_i is the regression parameter associated with the ith predictor variable such that odds ratio associated with increase in one unit of the ith variable, when other variables are constant, is

$$\mathbf{OR_i} = e^{\beta_i}$$

We followed the following strategy:

We decided to identify the specific factors through a series of logistic and linear regression analyses. First, we performed crude analyses of each putative risk factor. Subsequently, we completed three multivariable regression analyses for each group of putative risk factors:
(i) Preoperative risk factors: To determine whether preoperative risk factors increase the risk related to CPBCS at 3 months after surgery, the independent variables included in the analysis were age, preoperative pain, anxiety, and depression. The score of anxiety (GAD-7) and depression (PHQ-8) were calculated by summing 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 corresponded to mild, moderate, and severe depression, respectively.
(ii) Intraoperative factors: we included type of surgery and axillary status as independent variable.
(iii) Postoperative factors: acute pain, radiotherapy and chemotherapy were included as independent variables

Next, we performed one multivariable regression analysis including all potential risk factors. We did these analyses to prevent any bias from being introduced by controlling an intermediary variable instead of a confounder. For example, if preoperative pain is a predictor for acute postoperative pain, and the latter predicts CPBCS, including both independent variables in the model will not allow us to identify preoperative pain as a predictor for CPBCS if all its effect is carried through acute postoperative pain. By combining all variables in the final model, and

comparing to the previous models, we can evaluate if the effect of each variable is modified by other risk factors. Lastly, the final model only included the factors significantly related to CPBCS [odds ratio (OR) or regression coefficients (β)], factors with a significant effect (OR > 2) but without statistical significance, and confounders. The evaluation of the confounders was based on the change-of-estimate criterion that compares the difference between the adjusted and crude effects for a given factor, with the cut-off for an important change set at 10%. Pearson correlation was also used to assess the correlation between dependant variable and all candidate risk factors. All analyses were performed with SAS 9.4 software (Statistical Analysis System; SAS Institute Inc, Cary, NC, USA).

In both 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), surgery type (mastectomy segmental = 1, mastectomy = 2), axillary status (sentinel lymph node biopsy = 1, axillary dissection = 2), acute postoperative pain [no or mild (NRS $\leq$ 3) = 1 , moderate and severe (NRS >3) = 2], radiotherapy (no = 0, yes = 1), and chemotherapy (no = 0, yes = 1) were entered as dichotomous variables. Age was entered as continuous variable.

5. MANUSCRIPTS

5.1 Risk factors related to chronic pain after breast cancer surgery: A systematic review

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Abstract

Aim: To conduct a systematic review to identify the potential risk factors related to chronic pain after breast cancer surgery (CPBCS). CPBCS is a significant clinical concern affecting 13%-93% of patients. Many pre-, intra- and post-operative factors have been postulated as potential risk factors, but it is not clear which factors are implicated in CPBCS. ***Methods***: The literature search was undertaken for the period from January, 1995 to April, 2015 using Medline, Cochrane Central Register of Controlled Trials, CINHL and EMBASE databases. Articles were considered relevant if they included breast cancer surgery, had assessed CPBCS or assessed the perioperative therapy to prevent CPBCS. ***Result***: We identified 2398 publications and 84 were included in this review. From those, 23 were randomized clinical trials, 26 retrospective cohort and 21 prospective cohort studies. Surprisingly, the definition of CPBCS was only specified in 22 studies, where the most common definition was persistent pain three months after surgery. Thirty-seven percent (37%) of studies investigated the neuropathic nature of CPBCS. The most commonly assessed risk factors were age (45 studies), radiotherapy (36 studies), chemotherapy (36 studies), type of surgery (33 studies) and axillary lymph node dissection (30 studies). The risk factors identified by more than 20% of the studies were: axillary lymph node dissection (24/30; 80%), comorbidities (11/15; 73.33%), acute postoperative pain (6/9; 66.67%), young age (< 55 years) (19/45; 42.22%), depression (4/10; 40%), anxiety (4/10; 40%), radiotherapy (12/36; 33.33%), and chemotherapy (9/36; 25%). ***Conclusion***: Axillary lymph node dissection, preoperative pain and acute postoperative pain contribute to CPBCS. The role of adjunctive therapy, psychological factors and complications after surgery remains unclear because of the methodological limitations of the reviewed studies.

Introduction

Breast cancer is the most common cancer in women worldwide[1] and represents 12% of all new cancer cases in women. Early diagnosis and novel surgical treatments have considerably increased the five year survival rate of breast cancer patients. However, breast cancer patients frequently develop chronic pain after surgery (CPBCS) with the prevalence ranging from 13% to 93%.[3] This represents a significant clinical involvement having a strong impact on the patients' quality of life.[25]

The etiology of CPBCS is unclear.[114] Multiple putative risk factors such as age, perioperative pain, genetics, psychological factors, type of breast surgery, cancer status, postoperative complications and adjunctive therapy have been reported in the development of CPBCS. Nevertheless, a systematic review (SR) including studies from 1995 to 2010 (n = 60) on risk factors related to CPBCS revealed nerve damage and radiotherapy as significant predictors for CPBCS.[4] This SR,[4] however, concluded that there were several methodological limitations within the available literature. In the meantime, a plethora of articles, most being prospective, have been published to assess the risk factors related to CPBCS. Therefore a review of the available literature, including a number of recently published studies was indicated.

Thus, the objectives of this systematic review were to: (i) identify the potential risk factors related to CPBCS; and (ii) perform a quality assessment of the recent available literature.

Method

Literature search

The search was undertaken with the collaboration of Martin Morris, librarian at McGill University, using Medline Ovid, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and EMBASE databases. The search strategy used is shown in table 5-1-1.

Studies published regarding CPBCS were identified. Medline yielded 364 articles, Cochrane library 85 articles, CINAHL 645 articles and EMBASE 1304 articles. Seventeen duplicates were removed and articles were screened by their titles and abstracts. The remaining 162 articles (92 from Medline, 1 Cochrane article, CINAHL 23 articles and 46 from EMBASE) were read; of

those, 84 papers following the eligibility criteria were ultimately included in this review (Figure 5-1-1). The search strategy followed the Cochrane recommendation and the report for our systematic review was prepared in compliance with the PRISMA guidelines. Figure 5-1-1 presents the PRISMA flow diagram summarizing the selection process for studies included in this systematic review.

Table 5-1-1: Search strategy	
1. exp Breast Neoplasms/	7. exp Chronic Pain/
2. exp Mastectomy, Segmental/ or Breast conservative surgery.mp.	8. ((chronic* or persistent* or long-term* or cancer) adj3 pain).tw.
3. Sentinel lymph node biopsy.mp. or exp Sentinel Lymph Node Biopsy/	9. ((post-mastectomy or postmastectomy) adj3 pain*).tw.
4. exp Sentinel Lymph Node Biopsy/ or Axillary lymph node dissection.mp.	10. (neuropathic* adj3 pain*).tw.
5. Intercostobrachial nerve.mp.	11. 7 OR 8 OR 9 OR 10
6. 1 OR 2 OR 3 OR 4 OR 5	12. 6 AND 11
13. Limit 12 to (yr="1995 - 2015" and English)	14. Limit 12 to (yr="1995 - 2015" and French)

Eligibility criteria

Articles were included if: (1) the study population had undergone breast cancer surgery and the study outcome was CPBCS; (2) the study assessed the risk factors related to CPBCS or the study assessed the perioperative therapy to prevent CPBCS. Papers were excluded if they were related to treatment of CPBCS (Figure 5-1-1). Randomized clinical trials (RCTs) regarding treatment of CPBCS were excluded as our intent was to assess the risk factors that contribute to CPBCS and the risk factor needs to precede the onset of CPBCS. Articles in languages other than English and French were excluded. Furthermore, unpublished studies were also excluded from this review. This decision of excluding unpublished studies was based on the study by Egger et al. (2003),[115] who showed that the methodology and quality of reviewed papers is better than including gray literature such as abstracts, which are usually of poorer quality.

Validity assessment

The methodological quality of RCTs was rated by using recent CONSORT guidelines, and observational studies were assessed by using an 18-item checklist that has been extensively used in previous studies.[3,116-119] All articles were independently assessed and scored by two reviewers

Ana Velly (AV), Harsimrat Kaur (HK) and in case of disagreement, consensus was achieved by discussion.

Data extraction

Two reviewers (AV and HK) independently extracted data on the risk factors related to CPBCS. Data extracted are included in tables 5-1-2 and 5-1-3.

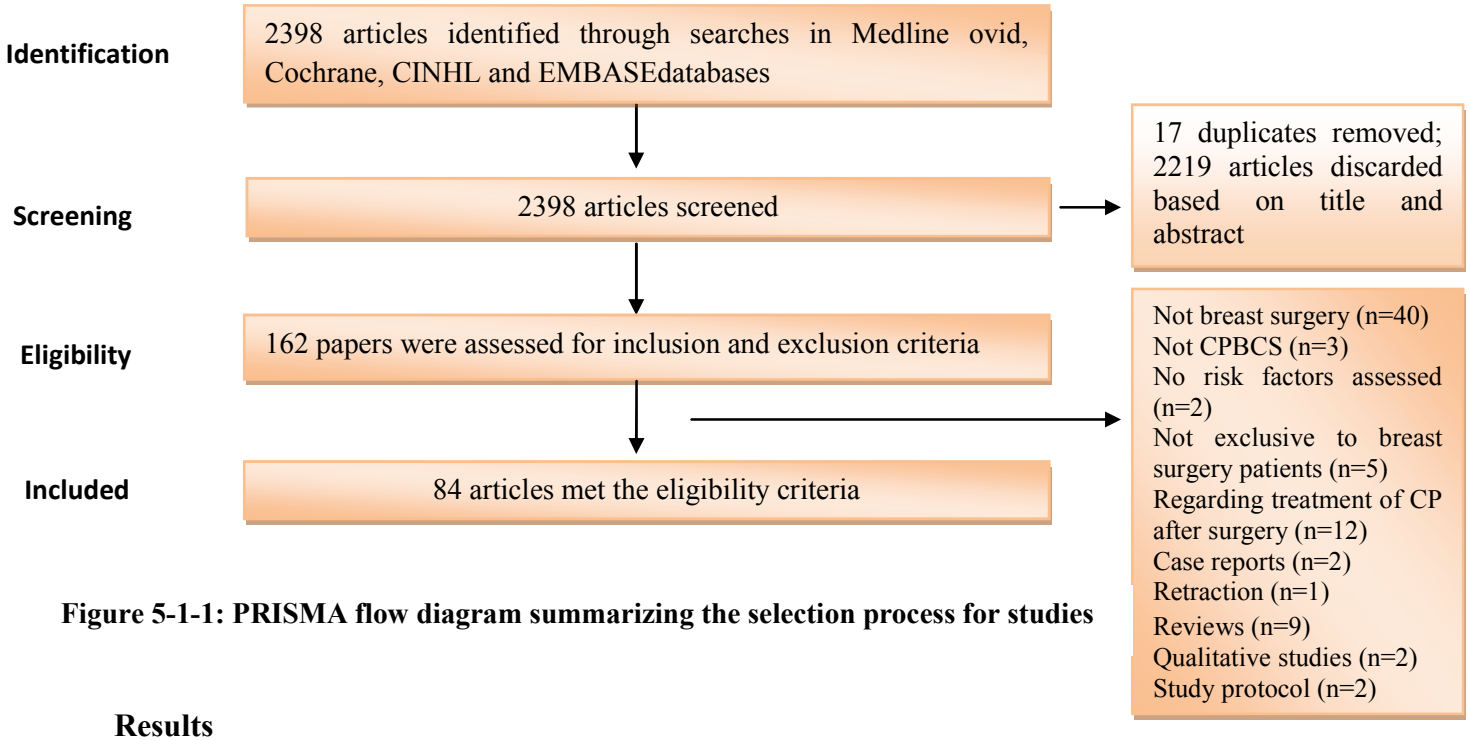

Figure 5-1-1: PRISMA flow diagram summarizing the selection process for studies

Results

We screened 2398 publications, and 84 were included in this review. From those, 23 were RCTs, 26 retrospective cohorts, 21 prospective cohort studies, 10 cross-sectional, three case-control studies, and one longitudinal study. Study characteristics and risk factors related to CPBCS are shown in Table 5-1-2 and 5-1-3.

Prevalence and nature of CPBCS

CPBCS prevalence ranges from 8% to 82%.[15,18,19,27-30] Variability in the estimates were due to differences in CPBCS definition, study designs, surgical techniques, analgesic strategies, and adjunctive therapies used. For example, prevalence of CPBCS was 8.2% in a retrospective cohort study[31] (n = 196) that considered only severe post operative pain (NRS≥5), 12 months after surgery.As well a prospective cohort study (n = 114)[22] that included all degrees of pain

intensity (NRS = 1–10) revealed a prevalence of 48.8%, 3 months after surgery. Neuropathic CPBCS, assessed by questionnaires (LANSS and DN4) and quantitative sensory testing (n =? 3),[5,34,36] showed prevalence ranging from 8.3% to 33.8%.[5,18,34,36,82]

Preoperative factors studied by various authors are:

Genetics

Only one prospective cohort study[11] investigated the association between genetic makeup and CPBCS at 6 months after surgery using multivariable analyses. Patients with interleukin [IL] 1 receptor 2 rs11674595 were at higher risk (OR= 36.1) to develop CPBCS ($p = 0.015$) than those without this receptor. In addition, patients with IL10 haplotype[11] were less likely to have CPBCS by 79% ($p = 0.037$) (Table 5-1-2).

Age

A positive relationship between young age (< 55 yrs.) and CPBCS was found in 42.22% (19/45) of studies.[5,6,17,22,29,30,32,40,50,52,65,72,75,80,83,85,88,90,96] The magnitude of the OR ranged from 2.01 to 5.23 (Table 5-1-2). Out of these 19 studies, eight were prospective cohort, eight retrospective cohort and three cross-sectional studies (Table 5-1-2). Prospective cohort studies with follow-up at 3 months,[22,80] and at ≥ 6 months,[29,30,50,88,90,96] revealed that young patients had an increased risk to develop CPBCS regardless of other risk factors. Similarly, retrospective cohort studies with ≥ 6 months[5,6,32,40,52,65,72,85] of surgery, showed young age to be related to CPBCS. It was interesting that one prospective cohort study[9] found older age (≥ 70) to be associated with CPBCS at 6 months after surgery using the Bayesian analyses.

Psychological factors

Four of 10 studies identified that anxiety[14-17]contributes to CPBCS. Among these were a 4 –year longitudinal study,[14] two cross-sectional,[15,17] and one case-control study[16] (Table 5-1-2). The magnitude of the OR was weak ranging from 1.12 - 1.83.

Four studies – 4-year longitudinal study,[14] 1-year retrospective cohort study,[13] cross sectional study[17] and case-control study[16] – demonstrated that depression was related to CPBCS regardless of other risk factors. The magnitude of the OR for depression ranges from 1.10 - 2.07.

Two studies[15,16] assessed catastrophizing as a risk factor for CPBCS. A case-control[16] showed that patients with catastrophizing were almost four times as likely to have CPBCS (OR = 3.46) as compared to a non-catastrophizing control group. A cross-sectional study[15] found a moderate correlation between catastrophizing (r = 0.43) and CPBCS after 3.2 years of surgery.

Those previous results, were not consistent with three prospective cohort studies with a large sample size (n>110).[22,90,91] The multivariable logistic regression analyses showed that patients exposed to higher levels of anxiety and depression were not more likely to develop CPBCS than patients without anxiety or depression at 3[22] and 12 months[91] of surgery ($OR_{anxiety}$ = 1.03; p = 0.97)(Table 5-1-2).

Comorbidities

A positive relationship between comorbidities and CPBCS was found in 73% (11/15)[9,11,17,20,22,30,35,36,47,79,87,88,90,91,97] of studies, with the magnitude of the OR ranging from 2.53[17] to 8.71,[11] where analyses were adjusted for other risk factors (Table 5-1-2). More specifically, preoperative pain (OR = 2.90; $p < 0.001$),[9] diabetes mellitus (OR = 2.61; p = 0.002),[98] diabetic neuropathy (OR = 8.17; $p < 0.0001$),[98] and fibromyalgia (OR = 2.64; p = 0.03)[98] were associated with an increased risk of CPBCS after 6[9] and 9[98] months of surgery. Out of these 11 studies, six were prospective,[9-11,14,90,91] three retrospective,[20,47,87] and two cross-sectional[17,79] studies (Table 5-1-2).

However, 3-month[22] and 6-month[11,30] prospective cohorts studies including 95 to 410 women with breast cancer did not find that preoperative breast pain (OR = 0.84; p = 0.76), pain in other part of body (p = 0.54), and/or diabetes (p = 0.079) contribute to CPBCS, regardless of other risk factors.

In addition, a prospective cohort study[9] suggested that the CPBCS risk was modified by pre-operative pain intensity. Women with severe preoperative pain (>4; NRS 0-10) had increased risk (OR = 2.90; p < 0.01) to develop CPBCS, in comparison to those without preoperative pain after 6 months of follow-up.

Intra-operative factors assessed by various studies are:

Type of surgery

The results of this systematic review indicate that type of surgery e.g. breast-conserving surgery (lumpectomy) or mastectomy is not a predictor of CPBCS (Table 5-1-2).

Thirty-three studies have evaluated the impact of different types of surgery on CPBCS, only three studies found a positive relation between CPBCS and type of surgery. Out of these, two retrospective cohort studies at 12[12] and 32 months after surgery,[32] showed breast-conserving surgery to be related to CPBCS (OR= 1.68) regardless of other risk factors. On the contrary, one cross-sectional study[77] showed by pictogram that patients with mastectomy had an additional field of pain over the chest wall in comparison to those who underwent breast-conserving surgery.

Axillary lymph node dissection (ALD)

A positive ALD contribution was identified in the majority of the studies (80%) that evaluated ALD as a factor for the development of CPBCS, when compared to sentinel lymph node biopsy (SLB). Among those 24 positive studies, two were RCTs,[21,74] 19 cohort studies[29,30,43,46,48,50,51,54,56,59-62,66,70,72,90,91,96] and three cross-sectional studies. In these studies, CPBCS was defined at different duration of follow-up: 3,[56] 6[29,30,90] and >6 months.[43,46,48,50,51,54,59-62,66,70,72,91,96] The magnitude of effect found in these studies ranged from 1.22 to 7.7 (Table 5-1-2 and 5-1-3).

Intercostobrachial nerve (ICN)

Four RCTs[37,38,55,57] and four cohort[10,39,58,87] studies assessed the role of preservation of ICN (Table 5-1-2 and 5-1-3). From those, one 3-month RCT[55] and one retrospective cohort study,[58] where data was collected between 2.5 and 6 years after surgery, revealed that ICN incision was associated with CPBCS in comparison to ICN preservation (Table 5-1-2 and 5-1-3). However, three RCTs at 3 months,[38] 18 months,[39] and 3 year of follow-up,[37,38,57]and three cohort studies[39,96,98] at 9 months of follow-up with adequate sample size(n > 100) found non-significant results. Furthermore, one retrospective cohort study[39] (n = 150) did not find any increased risk of

development of CPBCS but CPBCS intensity was much more likely to be moderate or severe (3 point scale) in the nerve-divided group ($p< 0.0001$) (Table 5-1-2).

Perioperative pain management

Eighteen studies evaluated the effect of perioperative strategies on CPBCS prevention. In a parallel RCT,[42] Eutectic Mixture of Local Anesthetics (EMLA) decreased the incidence of CPBCS at 3 months after surgery. Another parallel RCT comparing Venlafaxine[76] and gabapentin showed that incidence of CPBCS was less at 6 months in the Venlafaxine group (26%) as compared to the gabapentin group (64%) (Table 5-1-3). Intravenous flurbiprofen axetil was effective in decreasing CPBCS in comparison to placebo ($p<0.05$) at 12 months of follow-up.[86] The use of perioperative lidocaine[92] infusion was also found to be associated with a decreased risk of CPBCS at 6 months after surgery (OR = 0.05; $p = 0.034$) (Table 5-1-3). Perioperative infusion of dexmedetomidine reduced the pain scores and the analgesic requirement during the first 72 h of observation and CPBCS at 3 months compared to control group ($p< 0.01$).[78] A parallel RCT[64] showed that EMLA and gabapentin have a positive effect on CPBCS at 3 months after surgery, decreasing the risk of CPBCS ($p = 0.028$).

Preincisional paravertebral block was shown to significantly decrease the risk of CPBCS at 2 ($p= 0.009$),[68] 6 ($p = 0.029$) and 12-months ($p = 0.003$)[18] follow-up when compared to the control group in a parallel RCT. As well, a RCT (n= 180; $p= 0.13$)[89] did not find any significant difference in the incidence of CPBCS at 6 months between the thoracic paravertebral block and placebo groups after breast-conserving surgery. Another RCT showed propofol to be effective in reducing CPBCS as compared with sevoflurane (OR= 2.55; $p = 0 .007$).[83]

Negative results are listed in Table 5-1-3. Two RCTs (n = 75; n = 100)[28,49] showed that regional block, mexiletine and gabapentin have no effect on CPBCS risk at 3 months of follow-up. In a RCT cross-over trial (n=25), Levetiracetam did not decrease the incidence of neuropathic CPBCS ($p= 0.83$).[73] A parallel RCT,[82] including 236 patients allocated to local wound infiltration with either ropivacaine or saline, did not find a positive effect on CPBCS at 3 months follow-up. A RCT[19] that used bupivacaine found that it did not have any effect on CPBCS[19] as compared to the control group at 9 months after surgery ($p= 0.66$) (Table 5-1-3).

Various post-operative factors assessed by various studies are:

Acute pain

Nine studies assessed the effect of acute pain in the development of CPBCS (Table 5-1-2), with six having a positive relationship. The risk identified by the prospective studies range between 1.34 and 2.02.[10,11] Furthermore, this risk appears to be elevated among individuals with severe acute pain (NRS >6) (Table 5-1-2). Patients exposed to moderate to severe acute pain present an increased risk of CPBCS (NRS $\geq$5) compared to those with mild acute pain.[10] In addition, severity of acute pain also contributed to moderate to severe chronic pain at 4 and 9 months[10] after surgery where the model was adjusted for other risk factors (Table 5-1-2).

Radiotherapy

One third[12,13,17,25,32,47,65,69,72,75,91,92] of 36 studies showed that radiotherapy is associated with CPBCS (Table 5-1-2). A prospective cohort analysis of an RCT[92] demonstrated in multivariate analyses that patients undergoing radiotherapy had a significantly higher risk of CPBCS (OR= 28.62; p = 0.008) at six months after surgery. Whereas, another prospective cohort study,[30] including 300 participants, found that radiotherapy was associated with the development of CPBCS at six months after surgery, in a univariate model (p = 0.04). However this significant effect did not remain in the multivariable model (OR = 1.05; p =0.85) adjusted for age, axillary lymph node dissection and basal metabolic rate.

It is suggested that the risk between radiotherapy and CPBCS is modified by the dosage of radiotherapy. A retrospective cohort study[43] (n = 266) did not find an increased risk of CPBCS when they used radiation dosage of <50 Gy, after 6.6 years (median) of surgery. Two other retrospective cohort studies, where additional boost doses of radiotherapy were used, showed increased CPBCS risk at 12 months of surgery.[12,13]

Chemotherapy

Nine (25%)[17,32,41,72,79,88,90,91,98] of 36 studies suggested chemotherapy as risk factor for the development of CPBCS. Patients who underwent chemotherapy were two to three times as likely to develop CPBCS compared to patients without chemotherapy regardless of other risk factors (Table 5-1-2).[79,91]

The majority of studies,[12,13,30,31,45,47,50,52,56,59,60,77,91,92] however did not find an association between chemotherapy and CPBCS. Among those studies that described the drugs used for chemotherapy, two cross-sectional studies[83,85] demonstrated that chemotherapy with cyclophosphamide,[85] epirubicin,[85] fluorouracil[85] or paclitaxel[83] were not associated with CPBCS.

Hormonal therapy

Twenty one studies assessed endocrine therapy as a potential risk factor, and only one 4-year longitudinal study[14] showed that tamoxifen treatment increased the risk of CPBCS (p= 0.001) (Table 5-1-2).

Postoperative complications

Only two studies out of 10 confirmed the positive association of CPBCS and postoperative complications. In a retrospective cohort study (n = 467),[32] postoperative bleeding predicted CPBCS in the breast scar area at 32 months after surgery (Table 5-1-2). A cohort study[29] including 174 patients showed that women having tissue necrosis had 40% less chance of developing CPBCS (Relative Risk, RR = 0.60).

A prospective cohort[88] (n=1205) found that patients with lymphedema (p = 0.002) were more likely to have CPBCS as compared to patients without lymphedema, when the analyses were adjusted by age, chemotherapy and extent of tumor. Another prospective cohort study[29] revealed that lymphedema (RR = 1.54) and the presence of axillary web syndrome (RR = 1.70) increase the CPBCS risk at 6 months follow-up.[29] This risk, however, did not persist when the analyses was adjusted for age and axillary lymph node dissection.

Discussion

CPBCS is a prevalent and complex clinical problem regardless of follow-up time period. This systematic review advances the evidence that axillary lymph node dissection, preoperative pain, and acute postoperative pain are predictors of CPBCS.

Axillary lymph node dissection

Our and previous SR[4] demonstrated that axillary lymph node dissection is a risk factor for development of CPBCS. This increased risk was not confounded by other identified risk factors.

Preoperative pain and acute postoperative pain

Our review provides evidence, through cohort studies, that preoperative pain and acute postoperative pain increase the CPBCS risk independent of other risk factors. This is in agreement with the review by Katz and Seltzer,[120] indicating that preoperative and postoperative acute pain are the most consistent factors associated with development of chronic postsurgical pain.

Age

Forty-two percent of studies suggested that young age contributes to CPBCS. This could be due to the aggressive nature of tumors in young women, requiring more invasive therapy and other adjunctive therapies,[121] such as radiotherapy, that is also related to CPBCS.[122] Another reason may be that young patients are physically more active and thus pay more attention to mild pain, contrary to older patients who become more aware of moderate to severe pain.[9] Therefore, it is important to consider pain intensity in future studies.

Psychological factors

Even though the relationship between psychological factors and chronic pain appears to be evident, it has been difficult to demonstrate the effect on CPBCS. Very few studies assessed the contribution of psychological factors (10/84 – anxiety and depression; 2/84- catastrophizing) in the development of CPBCS. From those studies, a positive association between CPBCS and psychological factors (anxiety and depression) was found in cross-sectional[15,17] and case-control, [16] but not in cohort studies.[22,90,91] Cross-sectional and case-control studies are limited as it is not possible to establish whether the psychological effects are risk factors or consequences of CPBCS.[20] Thus, a prospective cohort study with sufficient sample size and baseline psychological evaluation is required to evaluate the relationship between the psychological factors and CPBCS.

Radiotherapy

Anderson and Kehlet SR[4] concluded that radiotherapy appears to be related to CPBCS. Our SR found a lack of association between radiotherapy and CPBCS in the majority of the cohort studies, regardless of the duration of the follow-up. It is possible that risk due to radiotherapy is modified by its dose. The literature[122] suggests that the incidence of brachial plexus injury (a precursor of chronic pain),[123] increases with radiotherapy doses greater than 60 Gy. Therefore, the limitation of the studies reviewed in the current literature is the lack of information about the dosage of radiation used to rule out any conclusion.[20,31,34-36,41,72,77] It is strongly suggested for future studies to provide information regarding dosage of radiation to assess the contribution of radiotherapy to CPBCS.

Chemotherapy

Animal models demonstrated that mitochondria in primary afferent sensory neurons are responsible for the effect of chemotherapy on CPBCS.[124] Zheng et al. described that chemotherapy induces impaired mitochondrial respiration and ATP production in rats, indicating a bioenergetics deficit, which is related to CPBCS.[125] This SR, however, did not find any evidence supporting chemotherapy as a risk factor for CPBCS since most of the studies did not find any significant risk. However, as the majority of the studies did not describe the type and dosage of chemotherapy, our SR cannot confirm the contribution of chemotherapy in the development of CPBCS.

Hormonal therapy

Post-menopausal breast cancer female patients with estrogen receptor positive status are candidates for therapeutic hormonal interventions. RCTs report[56] that 5–35 % of women taking aromatase inhibitors (first line hormonal therapy) experience musculoskeletal pain.[126] Nonetheless, their contribution in the development of CPBCS is not supported by the current literature review.

Type of surgery

Our SR found only three of 33 studies, two from the same authors, that presented a positive CPBCS risk related to type of surgery. This is in line with two SR on chronic postoperative pain.[4,8] Surgery risk may be modified by duration of the surgery, intraoperative nerve damage, axillary status, and different adjunctive procedures. Therefore, these covariates should be accounted for in the statistical analyses in future studies to clarify the role of type of surgery in the development of CPBCS.

Intercostobrachial nerve

Eight studies assessed ICN as risk factor for CPBCS. Out of these, only three identified ICN to be significantly related to CPBCS. However, the validity of the positive risk is questionable since the methodology used in these studies was not optimal (Table 5-1-2 and 5-1-3).

Perioperative pain management

Although the evidence favors preventive approaches, most of these RCTs did not completely follow the CONSORT Guidelines (Table 5-1-3). Thus, RCTs with good internal validity are required to outline the perioperative treatment strategy for CPBCS.

Genetics

There is a scarcity of published data on genetic makeup and CPBCS. Only one study by Stephens *et al*[11] suggested an association of interleukin [IL] 1 receptor 2 rs11674595 and IL10 haplotype with CPBCS. The results from this study had a large confidence interval (95% CI; 2.02 - 643.37) pointing towards a lack of precision in results. However, this study provided groundwork for future research related to genetics. A study with a large sample size having sufficient power is obligatory to detect the difference in genes.

Limitations

In our review we included only English and French publications that may have resulted in the exclusion of relevant literature. Furthermore, even though we used a vast array of literature search strategy, we may have inadvertently missed articles. In addition, our results could have

been affected by publication bias where authors are more likely to submit, or editors accept, positive rather than negative or inconclusive results.

We included randomized control trials as well as observational studies in this review. Twenty-six studies had retrospective and 10 cross-sectional designs. These designs have inherent limitations with more chance of selection bias, information bias and confounders affecting the internal validity of the studies. Also, we noted major weaknesses in the RCTs reviewed that prevents any definitive conclusions on the effectiveness of perioperative pain management on CPBCS. Only seven out of 23 RCTs have quality scores of more than 50% (Table 5-1-3). The major potential problems were: imprecise randomization and allocation concealment, eligibility criteria not clearly stated, unclear description of how/who assessed the study outcome, no mention of intention-to-treat analysis and poorly-described statistical analysis. Among observational studies, 15 out of 52 have quality scores of <50% (Table 5-1-2). Although there is an improvement in the reporting quality of observational studies in recent years, it is still suboptimal (Table 5-1-2). The most common problem from the studies (62/84) was the lack of CPBCS definition, which leads to information bias. Furthermore, no standard definition of chronic pain is seen in the literature. The IASP definition of chronic pain is pain that lasts three months beyond the normal healing time,[100] but studies have applied time frames ranging from two to six months postsurgery.[2] Most of the studies did not assess the CPBCS intensity. This can modify the association of risk factors on CPBCS. Type and dosage of drug was not provided by the majority of the studies for chemotherapy, radiotherapy and hormonal therapy, which could influence the relation of these risk factors and CPBCS.

Conclusion

CPBCS is a prevalent clinical problem. Numerous studies (n= 84) assessed the role of risk factors related to CPBCS. Axillary lymph node dissection, preoperative pain and acute postoperative pain contribute to development of CPBCS. The roles of adjunctive therapy, psychological factors and complications after surgery remain unclear because of the methodological limitations of the reviewed studies.

Table 5-1-2:Risk factors assessed related to CPBCS in Observational studies and their quality											
Author	**Design**	**Sample**	**Data collected**	**Demographi-cs**	**Physchological factors**	**Comorbidity**	**Surgery**	**Adjunctive treatment**	**Acute pain**	**Compli-cation**	**Quality Scores**
Tasmuth *et al.*[32]	RC	467	32m	**Age***	-	-	**BC>Ma***	**RTX,*** **CTX,*** HTX	POP	Bleeding, **Seroma***	66%
Stevens *et al.*[33]	CS	95	-	Age, Edu, MS,Ethnicity,Employment	-	-	-	-		-	40%
Tasmuth *et al.*[34]	PC	105	BeS,1m, 6m,12 m	-	-	-	BC=Ma	-	-	-	78%
Tasmuth *et al.*[12]	RC	509	10-54m,[S1] 12 m[S2]	Age	-	**Pain** (OR=1.57[BS] OR=1.65[IA])	**BC>Ma*** (OR=1.7[BS] OR=1.7[IA]), LNR,TFS, T size	**RTX*** (OR=2.2[BS] OR=2.3[IA]), CTX, HTX	**POP*** (OR=1.57[BS] OR=1.65[IA])	Comp	67%
Carpenter *et al.*[35,36]	RC	178	37.6 m^	Age, Race, MS, Income, Edu, Employment	-	Physical comorb	ST	RTX, CTX, HTX	-	-	40%
Maycock *et al.*[39]	RC	150	3 y[$]	-	-	-	**ICBN**[#]	-	-	-	33%
Smith *et al.*[40]	RC	511	6 y	**Age,*** Edu, BMI	-	-	-	-	-	-	53%
Tasmuth *et al.*[13]	RC	265	1 y	Age	Anx, **Dep*** (OR= 1.1)	-	T stage, ST, LNR	**RTX*** (OR=4.7), CTX, HTX	**POP*** (OR= 1.7)	Bleeding, Seroma, Infection	75%
Hack *et al.*[41]	CS	248	33.2 m^	**Age**[#]	-	-	TFS,**LNR,**[#]NLN	RTX, **CTX**[#]	-	-	50%
Johansen *et al.*[43]	RC	266	6.6y[$]	Age, Menopausal status	-	-	**AxP* (ALD)**	RTX, CTX, HTX	-	-	40%
Gottrup *et al.*[44]	CC	26	-	-	-	-	Sensory testing	-	-	-	33%
Kuehn *et al.*[45]	RC	396	34m^	Demographics	-	-	TFS, NLN, ES	CTX	-	-	40%
Schrenk *et al.*[46]	PC	70	17m, 15.4m	-	-	-	**AxP* (ALD)**	-	-	-	35%
Ververs *et*	RC	465	4.7 y^	Age,MS,Edu,	-	**Comorb***	ST	RTX,	-	-	67%

al.[47]				Employment, Insurance		(OR= 3.4)		CTX, HTX			
Ernst *et al.*[48]	RC	148	6-12m; 5y	-	-	-	ST, **AxP* (ALD)**	-	-	-	60%
Swenson *et al.*[50]	PC	261	1m,6m,12 m	**Age,*** BMI	-	-	ST, **AxP* (ALD)**	CTX	-	-	59%
Haid *et al.*[51]	RC	235	25m, 18m		-	-	**AxP* (ALD)**	-	-	-	33%
Caffo *et al.*[52]	RC	757	12m	**Age***	-	-	ST, LNR	CTX	-	-	33%
Peintinger *et al.*[54]	PC	56	BeS; 7d; 9-12 m	-	-	-	**AxP* (ALD)**	-	-	-	65%
Schijven *et al.*[56]	RC	393	3m- 3y	Age	-	-	ST , **AxP*(ALD** OR = 3.23), T stage, TFS	RTX, CTX, HTX	-	-	67%
Taylor[58]	RC	208	2.5-6 y	-	-	-	**ICBN***	-	-	-	55%
Reitman[59,60]	PC	204	BeS; 1y, 2y	-	-	-	**AxP* (ALD)^{2y}**	-	-	-	71%
Leidenius[61]	RC	274	3y	-	-	-	**AxP* (ALD)^{IA}**	-	-	-	33%
Barranger[62]	PC	115	20.3m	-	-	-	**AxP* (ALD)^{IA}**	-	-	-	47%
Karki*et al.*[63]	RC	110	6m, 12m	-	-	-	**BC > Ma*^{AxP} BC >Ma*^{BS}**	-	-	-	53%
Macdonald *et al.*[6]	RC	138	9 y^	**Age**,***BMI***	-	-	TFS	-	-	-	41%
Gulluoglu *et al.*[65]	RC	85	6m	**Age***	-	-	ST	**RTX,***CTX,HTX	-	Comp	53%
Poleshuck *et al.*[22]	PC	114	BeS; 2d, 10d; 1m,3 m	**Age*** (OR = 0.95), Race, Edu, MS	Anx, Dep	Preop	**ST$^{\#}$**(β=0.24), T stage, Prior breast cancer	**RTX$^{\#}$** (β = 0.31), CTX	**Severe POP$^{\#}$** (β = 0.28)	-	67%
Schulze *et al.*[66]	RC	134	31.4m, 56.4 m	-	-	-	**AxP* (ALD)**	-	-	-	47%
Passavanti *et al.*[67]	PC	300	6m, 7m, 9m, 11m, 14m	-	-	-	**Ma+BR>Ma*$^{\#6}$** ^{m}Ma+BR>MRM$_{14m}$	-	-	-	71%
Ishiyama et al[69]	CS	247	3.8 y$^{\$}$	Age	-	-	ST, TFS, T stage	**RTX*** (OR=3.3), CTX	-	-	33%
Kudel	RC	504	20.4 m^	Age, Edu, MS,	-	**Preop,***	TFS,	RTX,		-	50%

et al.[20]				Race		phantom breast pain, scar pain	LNR, BR	CTX, HTX			
Langer *et al.*[70]	PC	449	31m[$], 29.5m[$]	-	-	-	**AxP*(SLB,** OR = 0.3)*[1A]	-	-	-	59%
Steegers *et al.*[72]	RC	495	23m[$]	**Age***	-	-	ST, **AxP*(ALD)**	**RTX,* CTX***	-	Comp	59%
Vilholm *et al.*[5]	RC	1032	18m	**Age*** (OR = 1.04), smoking	-	-	ST, AxP, **T location*** (OR = 6.48),**breast surgery earlier*** (OR= 8.12)	RTX, CTX	-	-	80%
Gartner *et al.* [75]	CS	3754	26m	**Age*** (OR = 3.62)	-	-	ST, **AxP*(ALD** OR= 1.77)	**RTX*** (OR=1.5), CTX	-	-	73%
Peuckmann *et al.*[25]	RC	1783	5 y	Age*(OR=0.5), BMI,Edu*(**less** OR=1.55), **MS*(single**, OR = 1.8)	-	-	ST, TFS	**RTX*** (OR =1.4)	-	-	60%
Fecho *et al.*[31]	RC	196	1m, 6-12m	Age,**Race*** (**non white**), insurance, obesity	-	Comorb	-	RTX, CTX	-	-	47%
Jud *et al.*[77]	CS	343	-	-	-	-	T size, nodal status, **ST* (Ma>BC)**	RTX, CTX, HTX	-	-	13%
Rief *et al.*[14]	L	3088	4 y	Age, **Edu*(higher education)**	**Dep,* Behavior variables,*** exercise	**Baseline pain score***		**HTX* (tamoxifen)**			67%
Fabro *et al.*[29]	PC	203	45d PO; 6 m	**Age*(**RR = 5.2), BMI, Employment, Edu	-	-	ST, **AxP*(ALD,** RR= 2.0)	RTX, CTX, HTX	-	Comp	71%
Sheridan *et al.*[79]	CS	111	64.5 m[$]	Age	-	**Preop*** (OR= 5.2)	ST, TFS	RTX, **CTX*** (OR=3), HTX	-	-	53%

Sipila *et al.*[9]	PC	553	BeS; 6 m	**Age***(OR=2.0), **BMI***(OR=3.4) **Smoking*** (OR =2.41), Alcohol	-	**Preop*** (OR=2.90), **CP*** (OR= 2.99)	**Previous operations*** (>4; OR= 2.91), ST, AxP, T stage	RTX, CTX, Preop use of HTX	-	Comp	83%
Bokhari F.N. *et al*[80]	PC	17	2d, 10 d; 3 m	**Age,*** gender, BMI	-	Preop	ST,**More invasive surgery***	-	**POP***	-	65%
Belfer *et al.*[15]	CS	1097	3.2 y	Age, Exercise, **sleep*** (β=0 .13)	**Anx*** (β= 0.26),Dep(β=**-** 0.14),C**atas*** (β=.47), **somatization*** (β=2.78),stress, Emotional stability	-	ST, AxP, BR	RTX, CTX	-	Comp	63%
Cho *et al*[83]	CS	228	2.5**-**4 y	**Age*** (OR = 0.95)	-	-	Surgery duration, **AxP***(**ALD** RR = 1.6)	RTX, HTX, **sevoflurane*** (RR=1.5)	-	-	67%
Mejdahl et al[85]	RCS	2828	2y, 6 y	**Age*** (OR =1.9)	-	-	ST, **AxP***(**ALD** OR = 2.0)	RTX, CTX	-	-	67%
Schreiber et al.[16]	CC	200	6m	Age, BMI	**Catas (OR=3.5),* Dep (OR =1.39),* Anx (OR =1.12),*** stress	-	AxP, ST,BR, Reoccurance	RTX, CTX, HTX	-	Comp	50%
Wilson et al[87]	RC	470	12 m	Age, **Race*** (AA OR=1.9)	-	DM (OR=1.9), FM (OR= 2.8)	ST, AxP, ICBN	RTX, **CTX*** (OR= 2.9)	-		47%
Bell et al[88]	PC	1683	1**-**5year	**Age,*** Edu,	-	-	ST, **Beyond stage 1*(**OR = 1.7)	RTX, **CTX*** (OR =1.74),HTX	-	**Lymph edema***	59%
Bruce et al[10]	PC	362	BeS; 1 w; 4m, 9 m	**Age*** (OR=0.91), BMI	**Optimism** (OR= 0.70)*	Preop	ST, **AxP***(**ALD**, OR= 2.97),[9m] ICBN	RTX, CTX, HTX	**POP*** (OR=1.34)[4m] (OR=1.17)[9m]	-	83%

DeOliveira, *et al*[30]	PC	300	6 m	**Age*** (OR=0.98), Height, Weight	-	Comorb	ST, surgical duration, **AxP*(ALD,** OR= 7.7), T stage, BR	RTX, CTX	-	-	65%
Stephens *et al*[11]	PC	516	2wks; 1- 6 m	**Genetics*** IL1(OR= 36), IL10(OR= 0.2), Age, Edu, MS,BMI, Exercise, Employment	-	Comorb, **Preop*** (OR= 8.7)	-	-	**Severe POP*** (OR =2.0)	-	76%
Miaskowski,*et al*[90]	PC	410	1m, 2m, 3m, 4m, 5m, 6 m	**Age,*** Edu,MS, **ethnicity***(non white), Income	Dep, Anx	**Preop***	ST, AxP*(**ALD)**	RTX**, CTX***	-	-	67%
Bredal et al[17]	CS	1332	2-6 y	**Age*** (OR=3.52), Edu, MS	**Anx***(OR=1.8) **Dep***(OR =2.1)	**Comorb*** (OR =2.5)	ST**, AxP*** **(ALD**OR=1.7)	**RTX*** (OR=1.69), **CTX*** (OR =1.87), HTX	-	-	63%
Meretoja *et al*. [91]	PC	970	12 m	BMI	Dep, Anx	**Preop*** (OR =0.70)	Previous operations, T size, LNR,**AxP*** (**SLD**,OR= 0.40)	HTX, **RTX*** (OR=0.51), **CTX*** (OR = 1.47)	-	-	78%
Shahbazi*et al.*[93]	CC	122	-	Age, BMI	-	-	-	-	-	-	53%

***,** Significant risk factor for CPBCS; [#] ,Significant factor for intensity of CPBCS;
Anx, anxiety; AA, African American; ALD,axillary lymph node dissection; AxP, axillary procedure; BeS, before surgery; BC, breast conservative surgery; BS, breast scar; BR, breast reconstruction; BMI, basal metabolic rate; CPBCS, chronic pain after breast cancer surgery; Catas, Catastrophizing; CC, case control; CP, chronic pain; CS, cross-sectional; Comp, complications; Comorb, comorbidities; CTX, chemotherapy; DM, diabetes mellitus; dep, depression; edu, education; ES, extend of surgery;FM, fibromyalgia; HTX, hormonal therapy; IA, ipsilateral arm; IBR,immediate breast reconstruction; ICBN, intercostals brachial nerve; L, longitudinal study; LNR, lymph nodes removed; MS, marital status; Ma, mastectomy; m, month;MRM, modified radical mastectomy; NLN, number of lymph nodes involved; PC, prospective cohort ; Po, post-operative; preop, preoperative pain; POP, post operative pain; QST, quantitative sensory testing; RCS, repeated cross-sectional study; RC, retrospective cohort; RTX, radiotherapy; RR, relative risk; SLB, sentinel lymph node biopsy; ST, surgery type; S1, sample 1; S2, sample 2; T location, tumour located in the upper lateral quarter;T size, tumor size; T stage, tumor stage; TFS, time from surgery; UA, unadjusted; wks, weeks; y, year;
^, mean; $, median

Table 5-1-3: Risk factors assessed related to chronic pain after breast cancer surgery in Randomized Controlled Trials and their quality						
Author	Sample	Follow-up	Groups studied		Risk factor assessed	Quality scores
Salmon *et al.*[37]	128	3m, 6m, 12m, 18 m	66	ICN+	ICBN	41%
			62	ICN -		
Abdullah *et al.*[38]	120	3m	40	ICN+	ICBN	41%
			80	ICN -		
Fassoulaki *et al.*[42]	46	0-6d; 3m	22	EMLA	**EMLA***	41%
			23	Co		
Fassoulaki *et al.*[28]	100	0-24h; 2-6 d; 3 m	22	R+M	Regional block, oral Mexiletine, and the combination of both	34%
			24	R+P		
			25	P+M		
			23	P+P		
Fassoulaki *et al.*[49]	75	0,3,6,9,24 h,3m	21	M+P	Gabapentin with an increased dose of Mexiletine	41%
			22	G+P		
			24	P+P		
Torresan *et al.*[55]	87	2d, 40d, 3m	42	ICN+	**ICBN***	28%
			43	ICN-		
Veronesi et al.[21]	200	6m and 24m	100	ALD	**AxP* (ALD)**^{6m,24m}	55%
			100	SLB		
Freeman[57]	120	3y	39	ICN-	ICBN	28%
			34	ICN+		
Fassoulaki*et al.*[64]	50	3h, 6h, 9h; 1-8d;3,6m	22	MA+G	**MA+G***	55%
			22	Co		
Kairaluoma *et al.*[18]	60	1m, 6m and 12 m	29	PV	**PVB***^{12m}	31%
			30	Co		
Iohom[68]	29	1, 2, 3, 4, 5d, 10w	15	Std anal(I)	**PVB***	41%
			14	PV (II)		
Eisenberg et al[71]	22	1m,3m,6m	9	Ama	Amantadine	38%
			8	Co		
Vilholm*et al.*[73]	27	-	25	-	Effect of Levetiracetam	80%
Bianco *et al.*[74]	374	6m, 12m, 18m, 24m	341	ALD	**AxP* [SLB**(OR = 0.5)]^{6m}	45%
			331	SLB		
Amr *et al.*[76]	150	4h,12h,24h; 2-10d; 6m	50	VG	**Venlafaxine and Gabapantin* (GG>VG)**	48%
			50	GG		
			50	Co		
Elkaradawy*et al.*[19] 2012	50	24h; 1,3, 6 and 9 m	21	MA	Multimodal analgesia	34%

			22	Co		
Jain *et al.*[78]	86	72 h; 3m	34	De	**Dexmedetomidine***	59%
			35	Co		
Mohamed S A *et al.*[81]	140	2-48hr; 1 and 2 m	35	Co	clonidine + topical bupivacaine	45%
			35	BG		
			35	C1G		
			35	C2G		
Albi-Feldzer*et al.*[82]	236	6-24h;3, 6,12 m	111	RV	Age, BMI, anx, dep, ST, RTX,CTX,HTX, Ropivacaine	86%
			108	Co		
Sun et al[86]	60	2-48h; 2,4,6, 12m	30	Group F	i.v.**flurbiprofen axetil**[2*, 4*, 6*, 12m]	41%
			30	Co		
Chiu *et al*[27]	132	12 m	58	TPVB	TPVB and LA	83%
			60	LA		
Karmakar *et al*[89]	180	Po; 3, 6 m	60	GA	TPVB - GA (RR= 1); GA+TPVB (RR= .83); GA+CTPVB (RR= .80)	76%
			57	GA+TPVB		
			60	GA+CTPB		
Terkawi *et al.*[92]	71	6m	34	Li	**Li*** (OR .05),age, BMI, ST, AxP, **breast implant***(OR 16.19),CTX,**RTX*** (OR 28.62), HTX	72%
			27	Co		

BG, bupivacaine group; CTPVB, continous thoracic paravertebral Block; Ca, cases; Co, control; C1G, clonidine 150 + bupivacaine; C2G, clonidine250+bupivacaine; De,dexmedetomidine;Dbs,daybeforesurgery; EMLA,eutectic mixture of local anesthetics; GG, Gabapantingroup; G+P,gabapantin+placebo; GP, generalized pain; GA, general anesthesia; Group F, flurbiprofen axetil; ICN(+), intercostobrachial nerve preserved; ICN(-), intercostobrachial nerve sacrificed; ICNU, intercostobrachial nerve status unknown; LA, local anaesthesia;; MA, multimodal analgesia; MA+G, multimodal analgesia + gabapentin; PV, paravertebral block; Pr, propofol; P+M, placebo+ mexiletine; P+P, placebo + placebo; R+M, regional block +mexiletine; R+P, regional block + placebo; Re, reference group; RP, regional pain; RV, ropivacaine; SP, severe pain; Se, Sevoflurane; SLB, sentinel lymph node biopsy; SLB-ALD, sentinel lymph node biopsy followed by axillary lymph dissection; TPVB, thoracic paravertebral block; VG, Venlafaxine

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

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Abstract

Aim: Chronic pain after breast cancer surgery (CPBCS) is a significant clinical problem affecting 13% to 93% of patients; 5% to 10% of these CPBCS patients are estimated to suffer from severe and disabling CPBCS. Thus, the aim of this prospective cohort study was to identify pre-, intra- and post-operative factors related to the risk and intensity of CPBCS three months after surgery.

Methods: Ninety-five female patients scheduled to undergo breast cancer surgery were recruited from the Jewish General Hospital, Montreal, Quebec. Age, preoperative pain, anxiety, and depression were assessed before surgery. Telephone follow-up interviews were conducted at seven days and three months after surgery to assess the acute postoperative pain and CPBCS, respectively, using the brief pain inventory scale. Data regarding type of surgery, axillary status, radiotherapy and chemotherapy was assessed from physicians' charts. Multivariable logistic regression and linear regression analyses were used to identify the factors implicated in CPBCS risk and CPBCS intensity respectively, at three months follow-up.

***Results*:** Eighty-two participants completed the follow-up three months after surgery. From those, 45 (55%) reported CPBCS, and 24 participants (53.33%) had moderate pain (NRS 3–7). In the multivariable analyses only preoperative pain (odds ratio (OR) = 4.41, $p = 0.03$) increased the CPBCS risk three months after surgery. CPBCS intensity at three months after surgery was positively related to depression ($\beta = 1.55$; $p = 0.0005$), and chemotherapy ($\beta = 1.34$; $p = 0.006$).

Conclusion: Our results demonstrate that preoperative pain increases the risk of CPBCS. Depression and chemotherapy contribute to CPBCS intensity. Therefore, these factors should be considered important to be evaluated and managed in order to reduce the burden of CPBCS.

Keywords: CPBCS, pain, risk factors, breast cancer, preoperative pain, acute pain, depression, chemotherapy

Introduction

Breast cancer is the most frequent type of cancer among women and represents 12% of all new cancer cases in women.[1] Chronic pain is a significant clinical problem after breast cancer surgery (CPBCS). Even though advancements in surgical techniques have rendered surgical procedures less invasive in order to prevent CPBCS,[2] its prevalence remains high (ranging from 13% to 93%).[3] Furthermore, 5% to 10% of CPBCS cases are estimated to suffer from severe and disabling CPBCS[4,5] diminishing the patient's health-related quality of life.[6]

The etiology of CPBCS is not well understood.[7,8] A number of putative risk factors for the development of CPBCS have been suggested, such as pain before[9] and early after surgery,[10-13] psychological factors,[14-17] type of breast cancer surgery,[18-21] adjunctive radiotherapy,[12,13,17] adjunctive chemotherapy,[17,22] and age.[5,6,10] However, due to several methodological limitations found in the available literature, it remains unclear which factors contribute to CPBCS. For example a large number of studies were conducted retrospectively and lacked a clear description of the study population and outcome, which may potentially decrease the internal validity of the studies. A literature review[4] conducted in 2011 emphasized the need to conduct a prospective cohort study to identify the risk factors related to CPBCS.

In a response to this gap in research, the primary aim of this study was to identify preoperative (age, preoperative pain, anxiety, and depression), intraoperative (type of surgery and axillary status) and postoperative (acute postoperative pain, radiotherapy and chemotherapy) factors that contribute to CPBCS onset three months following surgery. Our secondary aim was to determine if these pre-, intra- and post-operative factors were also related to CPBCS intensity three months after surgery. Intensity of chronic pain is relevant as it limits the abilities and activities of the patients to engage in their day-to-day life. To our knowledge only one other prospective cohort study[22] has assessed the risk factors related to CPBCS intensity.

Methods

Study design and population

This three months prospective cohort study was approved by the research ethics committee of the Jewish General Hospital (JGH), in Montreal, Canada. All participants were fully explained the purpose and intention of the study and those who agreed to participate signed a consent form.

Breast cancer patients were recruited from the Segal Cancer Center at the JGH. The inclusion criteria were: (i) women 18 years of age or older, (ii) who were incident cases of breast cancer and (iii) who were scheduled to undergo breast cancer surgery. The exclusion criteria were: (i) patients who did not undergo surgery; (ii) patients with a history of any other type of cancer; (iii) karnofsky performance status score under 50, which include patients who required considerable assistance and frequent medical care; (iv) metastases; (v) no access to a telephone; (vi) pregnant women; and (vii) males with breast cancer.

Assessment

Women who agreed to participate were invited to complete questionnaire assessing the putative risk factors within seven days before their surgery by Harsimrat Kaur (HK) or Shrisha Mohit (SM). Same investigators performed follow-up interviews by telephone –as in other studies[103-106] – at seven days and three months after surgery to evaluate putative risk factors and study outcome.

Putative risk factors

At the baseline assessment before surgery, participants completed a series of validated questionnaires[102,127] assessing preoperative pain, anxiety, and depression. To assess preoperative breast pain, participants were invited to respond to the question "Do you have pain or discomfort in your breast." Generalized Anxiety Disorder (GAD-7), and Physical Health Questionnaire (PHQ-8) were used to evaluate anxiety and depression, respectively with cut-off scores of 5 for mild, 10 for moderate, and 15 for severe condition.

Furthermore, acute postoperative pain was assessed by telephone interview at the seven day follow-up after breast cancer surgery using BPI.

Surgical data (type of surgery and axillary status) and data regarding adjunctive therapy (radiation therapy, and chemotherapy) were collected from the physician's chart (ChartMaxx, the electronic health record system at the JGH). Radiation treatment dose of 42.4 Gy was prescribed in 16 fractions to participants who underwent adjunctive radiotherapy.

Study outcome

CPBCS has been defined as pain present at three months following breast cancer surgery. This definition is supported by a statement by Kehlet *et al*. explaining that it is vital to select a conservative time frame of three months after the surgical procedure to have clinically relevant results.[101] CPBCS was assessed using the question; "Do you have pain in your breast, axilla or arm?" Pain intensity was assessed by three questions from the Brief Pain Inventory scale (BPI).[102] Pain intensity was defined as the average of the responses to three different questions from BPI (each scale is presented as a row of equidistant numbers where 0 = "no pain" and 10 = "worst pain possible"): "pain now," "average pain" and "worst pain" ratings.

Statistical analyses

All analyses tested a null hypothesis of no statistical relationship between the independent and dependent variables of interest at α=0.05 significance. Chi- square and Fisher exact test were used to compare the distribution of the categorical variables. To assess the means of the continuous variables Student's t test was used. We assessed the risk factors for the onset of CPBCS three months following surgery using a multivariable unconditional logistic regression analyses (proc logistic, SAS). Odds ratios (ORs) and their 95% confidence intervals (CI) were estimated. Crude and multivariable linear regression analyses (proc mixed, SAS) were employed to determine the contributors to CPBCS intensity three months following surgery. Regression coefficient (β) and their 95% confidence intervals (CI) were estimated.

We decided to identify the specific factors through a series of logistic and linear regression analyses. First, we performed crude analyses of each putative risk factor. Subsequently, we completed three multivariable regression analyses for each group of putative risk factors: (i) preoperative risk factors (age, preoperative pain, depression, and anxiety), (ii) intraoperative factors (surgery type and axillary status), and (iii) postoperative factors (acute postoperative pain, radiotherapy and chemotherapy). Next, we performed one multivariable regression analysis including all potential risk factors, preoperative factors, intraoperative factors, and postoperative factors in only one model. We did these analyses to prevent any bias from being introduced by controlling an intermediary variable instead of a confounder. For example, if preoperative pain is a predictor for acute postoperative pain, and the latter predicts CPBCS, including both

independent variables in the model will not allow us to identify preoperative pain as a predictor for CPBCS if all its effect is carried through acute postoperative pain. By combining all variables in the final model, and comparing to the previous models, we can evaluate if the effect of each variable is modified by other risk factors. Lastly, the final model only included the factors significantly related to CPBCS [odds ratio (OR) or regression coefficients (β)], factors with a significant effect (OR > 2) but without statistical significance, and confounders. The evaluation of the confounders was based on the change-of-estimate criterion that compares the difference between the adjusted and crude effects for a given factor, with the cut-off for an important change set at 10%. Pearson correlation was also used to assess the correlation between dependant variable and all candidate risk factors. All analyses were performed with SAS 9.4 software (Statistical Analysis System; SAS Institute Inc, Cary, NC, USA).

Results

Description of population

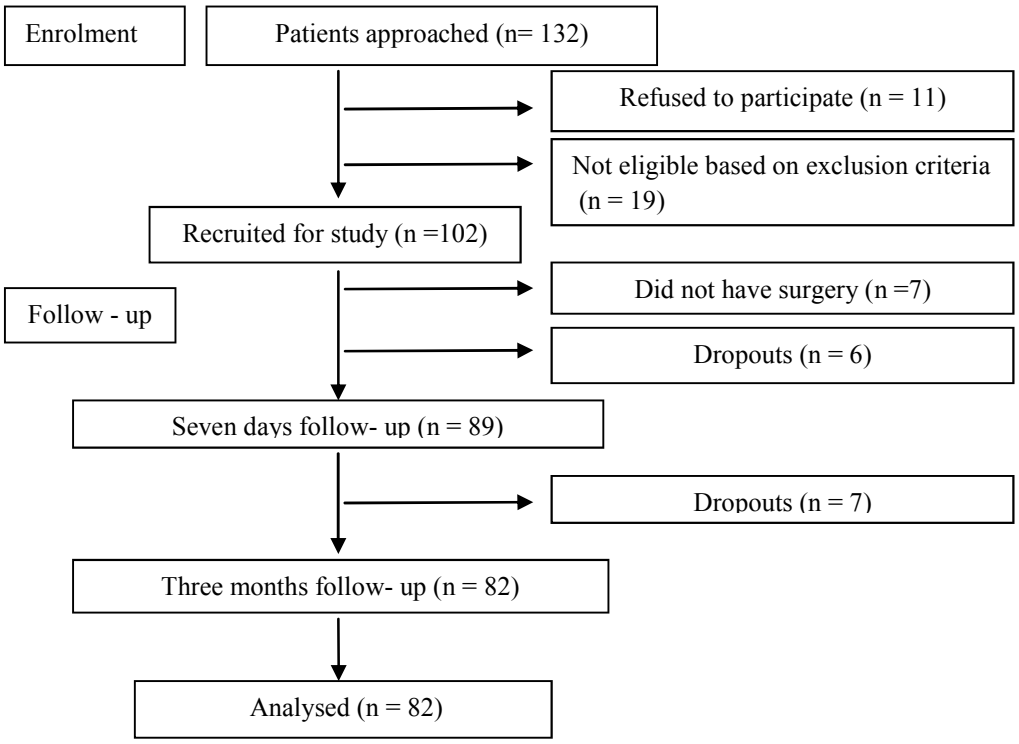
A total of 132 patients were invited to participate with 11 patients declining (participation rate = 92%). The main reason given for non-participation was lack of time. Of the 121 participants, 19 were excluded because they did not undergo surgery (n = 7), already had surgery (n = 8), was male (n = 1), could not read English or French (n = 1), and underwent breast reconstruction (n = 2). Out of 102 participants, seven patients did not undergo surgery and six patients refused to participate at seven day follow-up. Among the remaining 89 participants, 82 (86%) completed the three months' follow-up (Figure 5-2-1).

The 82 participants consisted predominantly of middle-aged females [mean age in years (SD) = 60.49 (13.94)]. Before surgery, 17 participants (20.73%) reported preoperative pain. The mean of the PHQ sum score was 5.41 [range (0-19)] and the mean GAD anxiety score was 6.12 [range (0-20)]. Thirty participants (36.59%) had PHQ score indicating moderate to severe depression, and 36 (43.90%) had GAD score indicating moderate and severe anxiety.

Most of the 82 participants received mastectomy segmental (n = 66, 80.48%). The mean (SD) acute postoperative pain at seven day after surgery was 3.0 (2.14). Postoperative radiotherapy

was given to 42 (53.85%) participants and less than half of the participants received adjunctive chemotherapy (n = 22).

Figure 5-2-1: **Patient enrolment and follow-up**



Predictors of onset and severity of CPBCS three months following surgery

At the three months follow-up interview, 45 (55%) of participants reported CPBCS and the mean pain intensity was 3.36 (SD = 1.74, 0-10 NRS). Moderate pain intensity (NRS 4-7) in the breast region (breast, arm and axilla) was reported by 53.3% of participants, and only one patient reported severe pain.

Tables 5-2-1 to 5-2-4 show the logistic regression analyses and Tables 5-2-5 to 5-2-8 the linear regression analyses, determining the predictors for the onset and severity of CPBCS at three months follow-up, respectively.

Preoperative factors

Participants with preoperative pain at baseline more frequently developed CPBCS (76.5%) than those without pre-operative pain (49.2%, p = 0.04). Based on these findings, participants with

pre-operative pain were more likely to develop CPBCS three months following surgery (OR = 3.35; p = 0.05). When the analysis included all other putative preoperative risk factors, preoperative pain effect remained borderline (OR = 3.33; p = 0.07). The final multivariable preoperative analysis indicates that only preoperative pain was associated with onset of CPBCS three months after surgery. We also found that preoperative pain risk (OR = 3.92; p = 0.06) was independent of the intraoperative and postoperative candidate risk factors. Our final multivariable analysis showed that participants with preoperative pain at baseline were 4 times as likely to develop CPBCS three months after surgery (OR = 4.11; p = 0.03) as those without, regardless of their axillary status, acute postoperative pain, and radiotherapy.

Preoperative pain, however, did not contribute to CPBCS intensity in the crude model (β = 0.43; p = 0.46), or in the multivariable linear model adjusted by preoperative risk factors (β = 0.03; p = 0.96), or by all risk factors (β = 0.73; p = 0.13). This change in β was due to correlations between preoperative pain and depression (r = 0.25, p = 0.09).

Age was not related to CPBCS risk three months after surgery in the crude analysis (OR = 0.99; p = 0.88), or in any multivariable logistic regression analyses (ORs = 1.00; p = 0.99 and p = 0.67). Also, no significant association was found between age and CPBCS intensity at three months after surgery in the crude model (β = -0.02; p = 0.45), multivariable models adjusted by preoperative risk factors (β = -0.003; p = 0.86) or by all risk factors (β = 0.02; p = 0.25).

CPBCS was more common among participants with moderate to severe depression (63.3%) than among those with mild or no depression (50.0%, p = 0.24). Moderate to severe depression at baseline was not related to the onset of CPBCS three months following surgery in the crude model (OR = 1.73; p = 0.24), in the multivariable preoperative model (OR = 2.16; p = 0.22), or in the multivariable logistic model including all putative risk factors (OR = 1.89; p = 0.34).

Participants with moderate and severe depression at baseline, however, were found to have significantly more intense CPBCS at three months after surgery than those without depression or mild depression (β = 1.56, p = 0.002). We found that the effect of depression on CPBCS severity remained close to 2 regardless of whether the model included only the preoperative factors (β =

1.76; $p = 0.006$), all candidate risk factors (β = 1.76; $p = 0.001$), or surgery type, chemotherapy and acute postoperative pain (β = 1.55; $p = 0.0005$).

The percentage of participants who developed CPBCS among those with moderate to severe anxiety at baseline (52.8%) was similar to those with mild or no anxiety (56.5%, $p = 0.74$). As expected, no significant association was found in the crude analysis (OR = 0.86; $p = 0.74$). This weak and non-significant association remained in the multivariable analyses including the preoperative risk factors (OR = 0.45; $p = 0.18$), and all putative risk factors (OR = 0.50; $p = 0.29$). In addition, no significant association was found between anxiety at baseline and CPBCS intensity in the crude model (β = 0.56; $p = 0.29$), or in multivariable model adjusted by preoperative factors (β = -0.42; $p = 0.47$) or by all risk factors (β = - 0.73; $p = 0.16$) at three months follow-up. Anxiety was correlated with depression (r = 0.54, $p < 0.0001$), and with surgery type (r = 0.30, $p = 0.04$).

Intraoperative factors

No statistically significant difference was noted between the frequency of CPBCS among participants who received mastectomy (62.5%) and those who underwent mastectomy segmental (53.0%, $p = 0.50$). Crude (OR = 1.48; $p = 0.50$), and multivariable models including intraoperative factors (OR= 1.25; $p = 0.71$) or all putative risk factors (OR= 1.56; $p = 0.52$) revealed that mastectomy when compared to mastectomy segmental did not contribute to CPBCS onset three months following surgery.

Nevertheless, the crude model revealed that participants who underwent mastectomy had an increase in the average CPBCS intensity when compared to those who received mastectomy segmental (β = 1.25; $p = 0.04$). We found that this effect was not confounded by axillary status (β = 1.31; $p = 0.04$). However, this significant association did not remain in the multivariable model including all putative factors (β = 0.83, $p = 0.13$) or only chemotherapy, depression and acute postoperative pain (β = 0.57; $p = 0.27$). This was because type of surgery was correlated to chemotherapy (r = 0.25, $p = 0.10$) and chemotherapy to CPBCS (r = 0.46, $p = 0.002$).

CPBCS was more common among participants who underwent axillary lymph node dissection (77.8%) in comparison to those undergoing sentinel lymph node biopsy (52.0%, $p = 0.17$). In the

crude logistic regression analysis, participants who underwent axillary lymph node dissection were more likely to develop CPBCS three months following surgery than participants undergoing sentinel lymph node biopsy (OR = 3.22; p = 0.16). This risk, however, was not statistically significant. We found that this increased likelihood to develop CPBCS three months following surgery remains similar when the model also included type of surgery (OR = 3.04; p = 0.19), all other putative risk factors (OR = 2.64, p = 0.29), or when the analysis was adjusted by preoperative pain, acute postoperative pain and radiotherapy (OR = 3.33, p = 0.17). However, these results were not statistically significant. Axillary status did not have any effect on CPBCS intensity in crude (β = -0.04; p = 0.96), multivariable linear regression analyses adjusted by type of surgery (β = -0.36; p = 0.62), or adjusted by other putative risk factors (β = -0.23; p = 0.71).

Postoperative factors

The distribution of participants who developed CPBCS three months after surgery was greater among participants with moderate to severe acute postoperative pain seven days after surgery (66.7%) than those without acute postoperative pain (45.7%; p = 0.06). As expected, our crude analysis showed that participants with moderate to severe acute postoperative pain were twice as likely to develop CPBCS three months after surgery, as participants with mild or no acute postoperative pain (OR = 2.38, p = 0.06). The magnitude of this association remained in the multivariable model including other postoperative factors (OR = 2.23, p = 0.09), all putative risk factors (OR = 2.22, p = 0.12) or when the model was adjusted by preoperative pain, radiotherapy and axillary status (OR = 2.35; p = 0.08).

The crude (β = 0.95; p = 0.07), multivariable linear regression analyses adjusted by postoperative factors (β = 0.55; p = 0.25), by all candidate risk factors (β = 0.78; p = 0.07), and by chemotherapy, depression and surgery type (β = 0.77; p = 0.07), participants with moderate to severe acute pain had tendency to have more intense CPBCS.

The percentage of participants who developed CPBCS among those who underwent radiotherapy (62.2%) was higher, but not statistically significant different, than among those who did not undergo this treatment (46.0%, p = 0.14). No statistically significant association was found

between radiotherapy and CPBCS three months following surgery in the crude (OR = 1.94; p = 0.14), and in the multivariate model including postoperative risk factors (OR = 1.85; p = 0.19). Participants undergoing radiotherapy had twice the likelihood to develop CPBCS when the model adjusted by all putative risk factors (OR = 2.15; p = 0.14) or the final model including preoperative pain, axillary status and acute postoperative pain (OR = 2.18; p = 0.11). However, none of these ORs were statistically significant.

Radiotherapy was also not related to CPBCS intensity at three months follow-up in the crude (β = 0.49; p = 0.37), in the adjusted analyses including postoperative risk factors (β = 0.79; p = 0.11), or in the model with all other candidate risk factors (β = 0.70; p = 0.14).

No significant difference was found between the percentage of participants who developed CPBCS (56.5%) among those who undergoing chemotherapy and those who did not (54.2%, p = 0.85). Therefore, our crude analysis showed that chemotherapy was also not associated with CPBCS three months following surgery (OR= 1.10; p = 0.85). The likelihood to develop CPBCS remained very weak and non-significant in the multivariable analyses adjusted by postoperative factors (OR = 1.10; p = 0.86), and by all candidate risk factors (OR = 1.03; p = 0.97).

However, chemotherapy contributed to an increase in CPBCS intensity at 3 months follow-up in the crude analysis (β = 1.73; p = 0.002). This effect remained when the model was adjusted by postoperative risk factors (β = 1.78; p = 0.002), and pre-, intra- and post-operative risk factors (β = 1.78 - 1.34; p = 0.0008 - 0.006).

Discussion

The results from this prospective cohort study showed that CPBCS is a significant problem with an incidence of 55%. From those cases, more than half of the participants [n = 24 (53.33%)] reported moderate pain (NRS 4-7) in the breast region (breast, axilla and arm). Preoperative pain emerged out as an independent predictor of CPBCS increasing the risk of CPBCS at three months follow-up. Depression and chemotherapy were positively associated with CPBCS intensity at three months after surgery.

The significant association between preoperative pain and CPBCS was expected, as cohort studies[9,11,20] demonstrated that participants with preoperative pain were 3 to 8 times as likely to have CPBCS as participants without preoperative pain. Our results is in agreement with previous systematic reviews[8,120] that indicated past pain is the most consistent factor associated with the development of CPBCS.

Depression and anxiety were not significantly associated with CPBCS. This is in agreement with other prospective cohort studies with large sample size (>110),[22,90,91] which showed participants exposed to higher level of anxiety[91] or depression[22] were not more likely to develop CPBCS. The studies that showed the positive association between psychological factors and CPBCS were cross-section[15,17] and case-control study designs.[16] The limitation of such study designs is that it is not possible to establish if the evaluated psychological factors are risk factors or a consequence of CPBCS. Although depression was not associated with CPBCS risk, it contributed to CPBCS intensity. This is in line with a study[128] where depressed chronic pain participants, relative to their non-depressed counterparts, reported greater pain intensity. It is suggested that depression amplifies pain and impairs patients' abilities to adapt with pain.[129] Thus, alleviating the depression could help to improve CPBCS intensity.

Other preoperative factor such as age was not a contributing factor for development of CPBCS risk and intensity. This finding is in accord with other studies[11,15,16,93,98] and a systematic review[4] that suggested that young age group patients were not at higher risk of developing CPBCS.

Majority of the available literature showed surgery type is not a predictor of CPBCS.[22,36,47,48,50,52,56,96] Our study also did not find that surgery type affects the risk and CPBCS intensity. Participants with ALND were three times as likely to have CPBCS as compared to participants who underwent SLB, but results were not statistically significant. This could be because of limited number of participants in ALND group (n = 9) in our study. As SLB is shown to be less morbid,[21] thus is used for patients with breast cancer in majority of the surgical units.[130]

Our study showed a borderline association between acute postoperative pain and CPBCS onset and severity at 3 months after surgery. Our findings support the results of available literature.[22] Acute pain is suggested to be a risk factor for a number of other chronic pain conditions. A positive association has been observed three (p = 0.0007) or six months (p = 0.0002)[131] after amputation, and 12 months after inguinal hernia repair ($p < 0.05$).[132] Thus, our study emphasizes the need to effectively treat acute pain to attenuate CPBCS risk and intensity.

Radiotherapy and chemotherapy did not significantly increase the CPBCS risk. Our results are consistent with previous studies[85,30,83] that also found no statistically significant role of radiotherapy and chemotherapy in the development of CPBCS. It is possible that the non-association found in our study was due to the total dosage of 42.4 Gy received by participants. Previous studies showed that radiotherapy dosage lower 60 Gy was not associated with brachial plexopathy, a predictor of chronic postoperative pain.[43,122] Nonetheless, chemotherapy was strongly related to CPBCS intensity. This is in agreement with a study[41] that showed participants on chemotherapy reported greater pain than participants who did not receive chemotherapy. It could be due to impaired mitochondrial respiration and ATP production, resulting in bioenergetics deficit.[125]

The findings from this study however should be interpreted in the context of its limitations. Our study did not have sufficient power to assess the role of axillary status, radiotherapy and acute postoperative pain. Secondly, there was great variation in the drugs and their dosage for chemotherapy, and considering the sample size of participants who received chemotherapy, we did not attempt to categorize chemotherapy based on drug type and dosage. Third, the association between risk factors and CPBCS could be biased by unmeasured confounding variables. Fourth, since 14% of the subjects did not complete the 3-months follow-up, there is a possibility for selection bias. There was a difference between participants who dropped out and those who completed the three months follow-up; participants who did not drop out reported more frequent preoperative pain, were more depressed, reported more severe acute postoperative pain, and underwent chemotherapy (Table 5-2-9). However, as this study is a prospective cohort study, this dropout may not obligatorily overestimate the effect, since subjects were enrolled before they have experienced the outcome of interest.

Our study has several strengths. First, we used a prospective cohort study design which ensures that risk factors and outcome misclassifications are non-differential and would attenuate estimates of association. Second, we performed a series of multivariable analyses adjusting for potential confounders. Third, we used validated instruments[102,112,113,127] for assessing outcome as well as for preoperative pain, acute postoperative pain and psychological factors, thus reducing the information bias.

In conclusion, CPBCS is a significant problem with an incidence of 55%. Preoperative pain is an independent predictor of CPBCS, and depression and chemotherapy were associated with CPBCS intensity, three months after surgery. This result suggests that preoperative pain, depression, chemotherapy and perhaps acute postoperative pain should be considered as an important factor to be evaluated and managed among breast cancer surgery patients in order to reduce the burden of CPBCS.

Table 5-2-1: Logistic regression analyses assessing preoperative predictors of CPBCS onset at 3-month follow-up (n = 82)

Risk factor	Category	CPBCS/ non-CPBCS (n)	Crude analysis	Multivariable analysis
			Odds ratio (95% Confidence Interval)	Odds ratio (95% Confidence Interval)
Age	Years	-	0.99 (0.97- 1.03)	1.00 (0.97- 1.03)
Pre-operative pain	No	32/33	1 (reference)	1 (reference)
	Yes	13/4	3.35 (0.99 - 11.37)*	3.33 (0.90 -12.34)**
Depression	No or Mild	26/26	1 (reference)	1 (reference)
	Moderate to severe	19/11	1.73 (0.69 - 4.34)	2.16 (0.63-7.37)
Anxiety	No or Mild	26/20	1 (reference)	1 (reference)
	Moderate to severe	13/9	0.86 (0.36 –2.07)	0.45 (0.14-1.45)
*p =0.05, **p =0.07, other p-values > 0.17				

Table 5-2-2: Logistic regression analyses assessing intraoperative predictors of CPBCS onset at 3-month follow-up (n = 82)

Risk factor	Category	CPBCS/ non-CPBCS (n)	Crude analysis	Multivariable analysis
			Odds ratio (95% Confidence Interval)	Odds ratio (95% Confidence Interval)
Type of surgery	Mastectomy Segmental	35/31	1 (reference)	1 (reference)
	Mastectomy	10/6	1.48 (0.48 - 4.53)	1.25 (0.39 –4.00)
Axillary status	SLB	38/36	1 (reference)	1 (reference)
	ALD	7/2	3.22 (0.63 -16.57)	3.04 (0.58 –16.05)
p values > 0.15				

Table 5-2-3: Logistic regression analyses assessing postoperative predictors of CPBCS onset at 3-month follow-up (n = 82)

Risk factor	Category	CPBCS/ non- CPBCS (n)	Crude analysis	Multivariable analysis
			Odds ratio (95% Confidence Interval)	Odds ratio (95% Confidence Interval)
Acute postoperative pain	No or Mild	21/25	1 (reference)	1 (reference)
	Moderate or severe	24/12	2.38 (0.96 – 5.88)*	2.23 (0.88-5.66)
Radiotherapy	No	17/20	1 (reference)	1 (reference)
	Yes	28/17	1.94 (0.80- 4.69)	1.85 (0.73 - 4.67)
Chemotherapy	No	32/27	1 (reference)	1 (reference)
	Yes	13/10	1.10 (0.42 - 2.89)	1.10 (0.39 - 3.11)
*p =0.06; other p values > 0.08				

Table 5-2-4: Multivariable logistic regression analyses identifying risk factors contributing to CPBCS onset at 3-months follow-up (n = 82)

Risk factor	Category	Multivariable (Model 1)	Final multivariable (Model 2)
		Odds ratio (95% Confidence Interval)	Odds ratio (95% Confidence Interval)
Age	Years	1.00 (0.97-1.05)	*Not included*
Pre-operative pain	No	1 (reference)	1 (reference)
	Yes	3.93 (0.97-15.88)**	4.11 (1.13-15.00)*
Depression	No or Mild	1 (reference)	*Not included*
	Moderate orSevere	1.89 (0.51-7.09)	
Anxiety	No or Mild	1 (reference)	*Not included*
	Moderate orSevere	0.50 (0.14-1.82)	
Type of surgery	Mastectomy Segmental	1 (reference)	*Not included*
	Mastectomy	1.56 (0.40-6.10)	
Axillary status	SLB	1 (reference)	1 (reference)
	ALD	2.64 (0.44-16.00)	3.33 (0.61 -18.23)
Acute postoperative pain	No or Mild	1 (reference)	1 (reference)
	Moderate or severe	2.22 (0.80-6.15)	2.35 (0.90-6.14)***
Radiotherapy	No	1 (reference)	1 (reference)
	Yes	2.15 (0.77-6.00)	2.18 (0.83- 5.69)
Chemotherapy	No	1 (reference)	*Not included*
	Yes	1.03 (0.32 -3.29)	

*p = 0.03,**p = 0.06, ***p = 0.08, other p-values > 0.10
Model 1: Multivariable logistic regression analyses including all the pre-operative, intra-operative and post-operative risk factors
Model 2: Final multivariable logistic regression analysis

Table 5-2-5: Linear regression analyses assessing preoperative predictors of CPBCS severity at 3-month follow-up (n = 45)

Risk factor	Category	Crude	Multivariable analyses
		β (95% Confidence Interval)	β (95% Confidence Interval)
Age	years	-0.02 (-0.05 – 0.02)	-0.003 (-0.04 – 0.03)
Pre-operative pain	No	1 (reference)	1 (reference)
	Yes	0.43 (-0.73 – 1.59)	0.03 (-1.10 – 1.16)
Depression	No or Mild	1 (reference)	1 (reference)
	Moderate or Severe	1.56 (0.60 – 2.51)*	1.76 (0.54 – 2.99)**
Anxiety	No or Mild	1 (reference)	1 (reference)
	Moderate or Severe	0.56 (-0.50 – 1.61)	-0.42 (-1.60 – 0.76)

*p = 0.002
**p = 0.006
Other p values > 0.28

Table 5-2-6: Linear regression analyses assessing intraoperative predictors of CPBCS severity at 3-month follow-up (n = 45)

Risk factor	Category	Crude	Multivariable analyses
		β (95% Confidence Interval)	β (95% Confidence Interval)
Type of surgery	Mastectomy Segmental	1 (reference)	1 (reference)
	Mastectomy	1.25 (0.04 – 2.46)*	1.31 (0.06 – 2.57)*
Axillary status	SLB	1 (reference)	1 (reference)
	ALD	-0.04 (-1.49 – 1.42)	-0.36 (-1.79 – 1.08)

*p = 0.04
Other p values > 0.61

Table 5-2-7: Linear regression analyses assessing postoperative predictors of CPBCS severity at 3-month follow-up (n = 45)

Risk factor	Category	Crude	Multivariable analyses
		β (95% Confidence Interval)	β (95% Confidence Interval)
Acute postoperative pain	No or Mild	1 (reference)	1 (reference)
	Moderate or severe	0.95 (-0.07 – 1.97)**	0.55 (-0.40 – 1.49)
Radiotherapy	No	1 (reference)	1 (reference)
	Yes	0.49 (-0.59 – 1.57)	0.79 (-0.19 – 1.76)
Chemotherapy	No	1 (reference)	1 (reference)
	Yes	1.73 (0.69 – 2.76)*	1.78 (0.72 – 2.84)*

*p = 0.002
**p = 0.07
Other p values > 0.10

Table 5-2-8: Multivariable linear regression analyses assessing predictors of CPBCS severity at 3-month follow-up (n = 45)

Risk factor	Category	Model 1	Model 2
		β (95% Confidence Interval)	β (95% Confidence Interval)
Age	years	0.02 (-0.01 – 0.05)	*Not included*
Pre-operative pain	No	1 (reference)	*Not included*
	Yes	0.73 (-0.23– 1.70)	
Depression	No or Mild	1 (reference)	1 (reference)
	Moderate Or Severe	1.76 (0.76 – 2.76)***	1.55 (0.71 – 2.36)*
Anxiety	No or Mild	1 (reference)	*Not included*
	Moderate or Severe	-0.73 (-1.76 – 0.30)	
Type of surgery	Mastectomy Segmental	1 (reference)	1 (reference)
	Mastectomy	0.83 (-0.26 – 1.92)	0.57 (-0.45 – 1.58)
Axillary status	SLB	1 (reference)	*Not included*
	ALD	-0.23 (-1.48 – 1.02)	
Acute postoperative pain	No or Mild	1 (reference)	1 (reference)
	Moderate or severe	0.78 (-0.06 – 1.63)*****	0.77 (-0.07 – 1.61)*****
Radiotherapy	No	1 (reference)	*Not included*
	Yes	0.70 (-0.24 – 1.63)	
Chemotherapy	No	1 (reference)	1 (reference)
	Yes	1.78 (0.79 – 2.77)**	1.34 (0.41 – 2.27)****

*p = 0.0005 ***p = 0.001 *****p = 0.07
**p = 0.0008 ****p = 0.006 other p values > 0.12
Model 1: Multivariable linear regression model including all putative risk factors
Model 2: Multivariable linear regression model including chemotherapy, depression, acute post-operative pain and type of surgery

Table 5-2-9: Difference among dropouts and participants who completed follow-up at 3 months after surgery (n = 95)

Risk factor	Category	Patients who completed follow-up	Dropouts	P value
Age	years	Mean (SD) 60.49 (13.94)	53.54 (11.34)	0.09
Pre-operative pain	No	n = 65 (68.42%)	n = 6 (6.32%)	0.01
	Yes	n = 17 (17.89%)	n = 7 (7.37%)	
Depression	No or Mild	n = 52 (54.74%)	n = 5 (5.26%)	0.08
	Moderate or severe	n = 30 (31.58%)	n = 8 (8.42%)	
Anxiety	No or Mild	n = 46 (48.42%)	n = 8 (8.42%)	0.71
	Moderate or severe	n = 36 (37.89%)	n = 5 (5.26%)	
Type of surgery	Mastectomy Segmental	n = 65 (68.42%)	n = 13 (13.68%)	0.07
	Mastectomy	n = 17 (17.89%)	n = 0 (0.00%)	
Axillary status	SLB	n = 73 (76.84%)	n = 13 (13.68%)	0.20
	ALD	n = 9 (9.47%)	n = 0 (0.00%)	
Acute pain	No or Mild	n = 46 (48.42%)	n = 13 (13.68%)	0.004
	Moderate or severe	n = 36 (37.89%)	n = 0 (0.00%)	
Radiotherapy	No	n = 37 (38.95%)	n = 12 (12.63%)	0.001
	Yes	n = 45 (47.37%)	n = 1 (1.05%)	
Chemotherapy	No	n = 59 (62.11%)	n = 13 (13.68%)	0.02
	Yes	n = 23 (24.21%)	n = 0 (0.00%)	

6. DISCUSSION

This section will provide a summary of the results, methodological considerations, strengths and limitations of this thesis.

Thus, the overall objective of this prospective cohort study was to identify the factors for CPBCS risk and intensity at 3 months after surgery. More specifically, our primary aim was to determine whether preoperative factors (age, preoperative pain, anxiety, and depression), intraoperative factors (type of surgery and axillary status) and postoperative factors (acute pain, radiotherapy and chemotherapy) increases the risk related to CPBCS at three months follow-up. Our secondary aim was to assess if these pre-, intra- and post-operative factors were related to CPBCS intensity at three months after surgery. To our knowledge, our study is one of the few studies that assessed role of risk factors on CPBCS intensity.

6.1 Summary of results

Results of this prospective cohort study showed that CPBCS is significant problem with incidence of 55%, out of which more than half of the patients [n = 24 (53.33%)] reported moderate pain (NRS 4-7) and one patient (2.22%) had severe pain (NRS >7) in the breast region.

6.1.1 Preoperative risk factors and CPBCS

Preoperative pain emerged out as independent predictor of CPBCS and increases the risk of CPBCS at 3-month follow-up. When the analysis included all other putative preoperative risk factors, preoperative pain effect remained borderline. The final multivariable preoperative analysis indicates that only preoperative pain was associated with onset of CPBCS three months after surgery. We also found that preoperative pain risk was independent of the intraoperative and postoperative candidate risk factors. Our final multivariable analysis showed that participants with preoperative pain at baseline were 4 times as likely to develop CPBCS three months after surgery as those without, regardless of their axillary status, acute postoperative pain, and radiotherapy. However, preoperative pain did not contribute to CPBCS intensity.

Age was not associated with CPBCS risk at 3 months after surgery in the univariate analyses, in multivariable analyses adjusted for preoperative factors and in multivariable analyses adjusted

for pre-, intra- and post-operative risk factors. Also, no significant association was found between age and CPBCS intensity at three months follow-up.

In multivariable analyses, patients with moderate and severe depression were at increased risk of developing CPBCS as compared to mild or absence of depression but results were not statistically significant. Nonetheless, patients with moderate and severe depression were found to have significantly more intense CPBCS as compared to mild or no depression. Univariate and multivariable analyses showed that moderate anxiety and severe anxiety were not significantly associated with CPBCS. In addition, no significant association was found between anxiety and CPBCS intensity at 3-month follow up.

6.1.2 Intra-operative risk factors and CPBCS

Our crude and multivariable models showed that the onset of CPBCS at 3 months follow-up was not related to the type of surgery (mastectomy vs mastectomy segmental). Nevertheless, there was a significant association between type of surgery and CPBCS intensity in the univariate model. This relation remains significant when model was adjusted by axillary status. However, type of surgery was no longer significantly associated when model was adjusted by all putative factors.

Based on logistic regression analyses, patients who underwent axillary lymph node dissection were more likely to develop CPBCS as patients with sentinel lymph node biopsy in the univariate, multivariable model including only the intraoperative factors, or other putative risk factors. However, these results were not statistically significant. Axillary status did not have any effect on CPBCS intensity in the univariate, multivariable linear regression analyses adjusted by type of surgery, or adjusted by other putative risk factors.

6.1.3 Postoperative risk factors and CPBCS

In a crude analysis, patients with moderate to severe acute postoperative pain were more likely to have CPBCS as patients with mild acute postoperative pain. This borderline association remained in the multivariable model adjusted by preoperative pain, radiotherapy and axillary status. In univariate, multivariable linear regression analyses adjusted by pre-, intra- and

postoperative risk factors, patients with moderate to severe acute postoperative pain has tendency to have more intense CPBCS.

No statistically significant association was found between radiotherapy and CPBCS in the univariate, and in the multivariate analyses including post-operative risk factors, all putative risk factors or the final multivariable model. Radiotherapy was also not related to CPBCS intensity at 3 months follow up in the crude, in the adjusted analyses including postoperative risk factors, or in the model with all other candidate risk factors.

Chemotherapy was also not associated with CPBCS in the univariate, multivariable analyses adjusted by postoperative factors, and in the multivariable model adjusted also for pre-, intra-, and post-operative risk factors. However, chemotherapy contributed to an increase in CPBCS intensity at 3 months follow up in the crude analysis. This effect remained when the model was adjusted by postoperative risk factors, and pre-, intra- and post-operative risk factors.

6.2 Methodological Considerations

Due to the systematic nature of errors (various types of bias) in a cohort study, incurring bias is always a possibility, as explained earlier. This section provides in-depth discussion of validity of the results.

6.2.1 Consistency with other studies

The significant association between preoperative pain and CPBCS was expected, as cohort studies[9,11,20] demonstrated that patients with pre-operative pain were 3 to 8 times as likely to have CPBCS as compared to patients without pre-operative pain. This study result is in agreement with a previous SR[120] that suggested past pain was the most consistent factor found to be associated with the development of CPBCS.

Although depression was not associated with CPBCS risk but it contributed to CPBCS intensity. This is in line with a study[128] where depressed chronic pain patients, relative to their non-depressed counterparts, reported greater pain intensity.

Our study showed a borderline association between acute postoperative pain and CPBCS onset and severity at 3 months after surgery. Our findings support the results of available literature.[22] Acute pain is suggested to be a risk factor for a number of other chronic pain conditions. A positive association has been observed three (p = 0.0007) or six months (p = 0.0002)[131] after amputation, and 12 months after inguinal hernia repair ($p < 0.05$).[132]

Chemotherapy was strongly related to CPBCS intensity. This is in agreement with a study[41] that showed patients on chemotherapy reported greater pain than patients who did not receive chemotherapy.

6.2.2 Bias

A bias is defined as any systematic error in any epidemiological study, which can result in incorrect estimation of association between the exposure and the disease. Thus, to increase the validity of cohort studies the investigator has to consider exposure, outcome, sample selection and the statistical analyses. Types of biases expected to occur in a cohort study are detailed below:

6.2.2.1 Selection bias

Selection bias refers to any error that arises in the process of identifying the study populations.[133] In order for this type of bias to occur, selection has to be related to both exposure and outcome. In this cohort study, subjects are enrolled before they have experienced the outcome of interest. Thus, factors affecting enrollment of subjects into a prospective cohort study would not be expected to introduce selection bias. However, retention of subjects may be differentially related to exposure and outcome, and this has a similar effect that can bias the results, causing either an overestimate or an underestimate of an association. We prevented bias from loss to follow-up in this study by maintaining high follow up rates (>80%). This was done by making questionnaires as easy to complete as possible, using telephonic follow- up interviews and maintaining the interest of participants and making them feel that the study is important. But there was a difference between patients who dropped out and those who completed the 3 months follow up; patients who did not drop out reported more frequent preoperative pain, were more depressed, reported more severe acute postoperative pain, and underwent chemotherapy (Table 5-2-9).

However, as this study is a prospective cohort study, this dropout may not obligatorily overestimate the effect, since subjects were enrolled before they have experienced the outcome of interest.

6.2.2.2 Information bias

Information bias is a type of systematic error in which the exposed and un-exposed group report exposure information differently for several reasons. It can arise from misrepresentation in the estimate effect due to measurement error or misclassification.[133]

Certain measures were applied to control information bias in our study. We used validated questionnaires to assess the independent variables and dependent variable. GAD-7, and PHQ-8 were used to assess anxiety, and depression, respectively. Their validity and internal consistency are high.[107-111] CPBCS was assessed using the question; "Do you have pain in your breast,arm and axilla?" and they were asked other three questions from the BPI[102] to assess the pain intensity. These questionnaires have excellent sensitivity, specificity and reliability.[102, 112,113]

There is no valid definition of CPBCS and the chance of misclassification needs to be considered. Outcome of the study (CPBCS) was defined clearly to prevent any misclassification. The frequency of CPBCS was similar to studies conducted in Finland,[9,91] Korea[83], Denmark[85] and Australia.[88] The frequency of CPBCS (55%) was found to be higher than reported by Bokhari F.N. *et al*. in Canada (24%).[80] But this study was limited in their sample size (n = 17).

6.2.2.3 Bias due to Confounding

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

6.3 Strengths

First, we used prospective cohort study design. Using this study design, it is almost certain that risk factors or misclassifications are non differential and would attenuate estimates of association. Second, potential confounders were adjusted in multivariable logistic regression analyses. Third, we used validated instrument for assessing outcome as well as for assessing baseline psychological factors.

6.4 Limitations

The findings from this study however should be interpreted in the context of its limitations. Our study did not have sufficient power to assess the role of axillary status, radiotherapy and acute postoperative pain. The justification for the number of participants included in our study, however, was based on the study feasibility (recruiting on average, 4 patients/week), and on the prevalence of common risk factors (e.g., mastectomy). We decided to base the sample size estimation on common putative risk factors, since we would like to utilize the current results to develop new strategies to largely prevent the incidence of CPBCS.

We found that by recruiting 76 patients (38 patients exposed and 38 nonexposed), considering that the occurrence of CPBCS among non-exposed is 35%, and the true relative risk is 2, our study is able to reject the null hypothesis (relative risk = 1), with probability (power) 83% (calculated by using PS version 3.0.43). We noted that this power remains if the number of non-exposed participants is twice than those exposed (24 patients exposed and 52 nonexposed, or vice-versa). This sample size/power analyses was conservative since it was based on relative risk (RR) 2 and, the prevalence of common risk factor (35%) was lower than that found in other studies.[22] Secondly, We decided to follow participants for three months after breast cancer surgery in this study, since the International Association for the Study of Pain (IASP) defines chronic pain as "pain without apparent biological value that has persisted beyond normal tissue healing time", which "in the absence of other criteria, is taken to be 3 months."[134] In addition, our decision for 3 months follow-up, is supported by Croft *et al*. (2010)[135] who stated that "this time reflects the most widely accepted time period." However, our ongoing study is following participants for three and six months. Our intention is to compare the incidence at these two times period.

Third, there was great variation in the drugs and their dosage for chemotherapy, and considering the sample size of participants who received chemotherapy, we did not attempt to categorize chemotherapy based on drug type and dosage. Fourth, the association between risk factors and CPBCS could be biased by unmeasured confounding variables. Fifth, since 14% of the subjects did not complete the 3-months follow-up, there is a possibility for selection bias. There was a difference between participants who dropped out and those who completed the three months follow-up; participants who did not drop out reported more frequent preoperative pain, were more depressed, reported more severe acute postoperative pain, and underwent chemotherapy (Table 5-2-9). However, as this study is a prospective cohort study, this dropout may not obligatorily overestimate the effect, since subjects were enrolled before they have experienced the outcome of interest.

7. CONCLUSION

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

1) CPBCS is a significant problem with an incidence of 55%.

2) Patients with preoperative pain are more likely to have CPBCS than without pre-operative pain, regardless of other preoperative, intraoperative and postoperative risk factors.

3) Depression and chemotherapy were associated with CPBCS intensity at three months follow-up, independent of other preoperative, intraoperative and postoperative risk factors.

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9. APPENDIX

(Consent form, and Questionnaire)

ACTION program

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

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

Period: baseline ☐

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

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

No ☐ Yes ☐

3) 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

5) 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

6) 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
☐	☐	☐	☐

ACTION program

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

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

Period: Day 7 after surgery ☐

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

No ☐ Yes ☐

2) 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

3) 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

4) 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

ACTION program

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

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

Period: Three months after surgery ☐

---

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

No ☐ Yes ☐

2) 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

3) 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

4) 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

Programme ACTION

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

Jour ☐☐☐ Mois Annee ☐☐☐ ☐☐☐☐ Hôpital ☐ Maison ☐

Période: référence☐

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1) Quel age avez-vous? _____ Ans

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

Non ☐ Oui ☐

3) 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 inquiétez ou de contrôler vos inquiétudes.	0	1	2	3
c) Inquiétudes excessive 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 est 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

4) 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

5) 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 ☐

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 lesein?

Non ☐ Oui ☐

2) 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

3) 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

4) 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

Programme ACTION

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

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

Période: Mois 3☐

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1) Vous avez des douleurs ou de l'inconfort dans lesein, région axillaire, bras?

Non ☐ Oui ☐

2) 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

3) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur la plus intense que vous ayez ressentie pendant les dernières **1 mois**.

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 **en général**.

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

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

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 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.
- Two telephone follow-up interviews will be conducted at 7 days and 3 months following your surgery. The interview can take on average 10 to 15 minutes for day 7 and 10 to 20 minutes for month 3. Your participation time will range from 4 to 5 months, depending on the time of your surgery.
- 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 centrifuge 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 impact 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 to the medical community with 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 after surgery.

Voluntary participation/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 decide to stop your participation 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:
While you take part in this research study, the researcher in charge and study staff will collect and store personal identifiable information about you in a file for the purpose of the research study. Only information necessary for the research study will be collected.

All information and saliva sample obtained about you 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 Dr. Velly's office at the Dental Department of the Jewish General Hospital. No information that discloses your identity will be allowed to leave the institution.

The saliva sample will be stored in the saliva freezer at the Lady Davis Institute of the Jewish General Hospital under the responsibility of Drs. Gornitsky, Schipper and Velly. Your sample will be stored until the saliva is used for study analysis. The remaining saliva sample will be destroyed in the laboratory of Dr. Hyman Schipper at the Lady Davis Institute, 10 years after the completion of the study. The sample will only be used for the purposes described in this consent form. The Lady Davis Institute requires a pass for entry, the door to the lab is locked and the results of the samples will be kept in a locked drawer with information being codified. Computer information is restricted by a password.

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 2932, 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. 5833.

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, and 3 months after surgery.

I agree to participate in this study.

_____

Printed name of participant

_____ _____

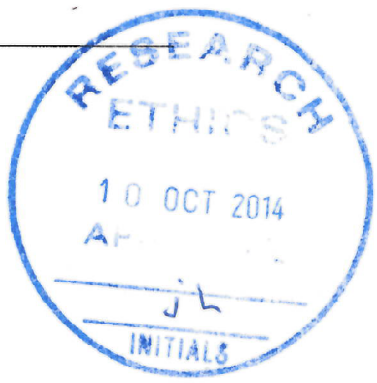
Signature of participant Date

_____

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 physique) 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.
- Deux entrevues téléphoniques de suivi seront effectuées 7 jours et 3 mois après votre chirurgie. Les entrevues peuvent prendre entre 10 à 15 minutes (entrevue jour 7), et 10 à 20 minutes (entrevue au 3ème mois) à compléter. Votre temps de participation dans cette étude sera entre 4 et 5 mois, dépendant de la date de votre chirurgie.
- 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.

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 2932, 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. 5833.

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, et 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