

# Assessing Gender Differences for Non-Predictable Breakthrough Cancer Pain Phenomenon: A Secondary Analysis from IOPS-MS Study

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**Purpose:** Breakthrough cancer pain (BTcP) is a temporary exacerbation of pain that “breaks through” a phase of adequate pain control by an opioid-based therapy. The non-predictable BTcP (NP-BTcP) subtype occurs in the absence of any specific activity. Evidence showed that gender differences exist in pain response sensitivity and clinical pain risk. This analysis aimed to signify the gender differences for the NP-BTcP phenomenon.

**Patients and Methods:** This is a secondary analysis of the Italian Oncologic Pain multiSetting-Multicentric Survey (IOPS-MS), the largest study on BTcP. The subset of NP-BTcP cases for non-gender-specific cancer was considered. Univariable and multivariate analyses were conducted to identify gender differences for the NP-BTcP profile about its intensity, number of episodes per day, and type. A metastatic status-stratified analysis was performed to compare gender with the main clinical variables among the population with NP-BTcP.

**Results:** Males exhibited a higher occurrence of BTcP in the thorax region compared to females (15% vs 11%, respectively,  $p = 0.03$ ). Males also had a higher onset of BTcP, a higher BTcP therapy dosage (33% vs 28%,  $p = 0.04$ , mean: 201 vs 186,  $p = 0.02$ ) and a lower Karnofsky score (mean: 46.9 vs 49.2,  $p = 0.03$ ) compared to females. Similar gender differences were found for metastatic patients in the BTcP site (14% vs 8.5%, respectively;  $p = 0.01$ ), peak onset (33% vs 27%,  $p = 0.02$ ), BTcP therapy dosage (199 vs 185,  $p = 0.04$ ), and Karnofsky score (mean 47.5 vs 50.4,  $p = 0.009$ ). Phenotype 2 was more characterized by non-metastatic males (41% vs 23%,  $p = 0.020$ ) while non-metastatic females presence was predominant among others.

**Conclusion:** In this study, gender differences according to site, onset and dosage of BTcP were found. The phenotype characterization of BTcP needs to be further investigated for a possible useful function in the management of cancer-related pain in non-metastatic patients.

**Keywords:** non-predictable breakthrough cancer pain, gender cancer pain, cluster analysis

## Introduction

Cancer pain is a debilitating condition and has severe effects on patients' quality of life.<sup>1,2</sup> The breakthrough cancer pain (BTcP) phenomenon represents a clinical peculiarity of cancer, which is characterized by a temporary exacerbation of pain that “breaks through” a phase of adequate control by an opioid-based therapy.<sup>3,4</sup> This

symptom can affect up to 70% of patients with cancer.<sup>5,6</sup> Notably, two types of BTcP have been recognized: predictable BTcP (P-BTcP) and non-predictable BTcP (NP-BTcP) that have different features according to pathophysiology, clinical and therapeutic involvements.<sup>7,8</sup> The P-BTcP is subdivided into three subgroups: the volitional BTcP (caused by a voluntary act), the non-volitional subtype (provoked by an involuntary act), and the procedural pain. The NP-BTcP occurs in the absence of any specific activity, which is also called idiopathic or spontaneous BTcP.<sup>9,10</sup>

Shreds of evidence demonstrate that men and women differ in their responses to pain. Specifically, women showed both greater sensitivity to pain and higher clinical risk than men; as reported by Bartley et al, many biopsychosocial mechanisms contribute to these sex differences in pain, including gender roles, sex hormones, endogenous opioid function and genetic factors.<sup>11</sup> In this paper, we described the results of a secondary analysis based on the Italian Oncologic Pain multiSetting-Multicentric Survey (IOPS-MS) focusing on gender differences regarding non-gender-specific cancer (No-GSC) from the NP-BTcP subset.

## Materials and Methods

### Details from IOPS-MS Dataset

Details concerning the enrollment of patients and all recorded variables have been previously described.<sup>7</sup> Briefly, the IOPS-MS study was a multicenter survey that involved 5 palliative care units (PCU), 7 oncology centers (ONC), and 9 outpatient pain clinics (OPC). The study was proposed by an expert group of 27 Italian centers representative of different settings of cancer pain and 21 centers agreed to participate. The primary aim of this study was to characterize BTcP in a large number of patients performed in different settings and to assess possible factors influencing its development. The secondary aim was to gather information about the diagnosis and management of BTcP as well as patient satisfaction with the treatment.<sup>7</sup>

The study protocol was approved by the local Ethical Committee, and informed consent was obtained from all patients enrolled in the study.

Inclusion criteria were: age greater than 18 years; diagnosis of cancer at any stage; well-controlled and stable background pain with an intensity  $\leq 4$  (on a 0–10 numerical rating scale, NRS); the presence of BTcP episode of moderate–severe intensity clearly distinguished from background pain. Exclusion criteria were as follows: no cancer diagnosis; unstable and/or uncontrolled background pain ( $>4/10$ ); no relevant peaks in pain intensity ( $<5/10$ ); poor collaboration or refusal to participate. Considering that in spontaneous BTcP more than 3–4 episodes per day usually indicate uncontrolled background pain (requiring a careful optimization of basal pain) we adopted the cut-off of 4 episodes per day.<sup>8</sup> Among all recorded variables from the original study, some variables were selected for this secondary analysis including age, gender, setting, BTcP site, therapies and dosages, onset, type of BTcP pain, Karnofsky performance status scale and type of physician. The study was observational and pharmaceutical therapies were used according to local policy, without following strict protocols. In our previous study, a multiple correspondence analysis (MCA) and a hierarchical clustering principal components analysis (HCPC)<sup>12</sup> were adopted to interpret the BTcP phenomenon on the original IOPS-MS dataset that included 2790 (69.6%) patients with NP-BTcP. The four clusters (phenotypes) represent a classification of patients based on BTcP status, defined by variables of BTcP intensity, number of episodes and type. Phenotypes were from P1 to P4 with the best group (P1) versus the worst one (P4) and with the same features.<sup>7,12</sup>

Briefly, P1 was characterized by older age ( $\geq 75$  years), slower onset ( $>10$  min), gastrointestinal as primary tumor, and greater propensity to be treated in the context of the palliative care setting. On the contrary, the main features of phenotype 4 were as follows: younger age ( $<55$  years) and rapid onset; furthermore, it most frequently concerns inpatients affected by lung cancer. Moreover, regarding the NP-BTcP therapy, the worst phenotype (P4) was mainly managed with rapid-onset opioids (ROOs); on the contrary, in phenotype 1 many patients were treated with oral, subcutaneous, or intravenous morphine. Moreover, the number of patients who did not receive therapy (ROOs, morphine and other therapy) decreased from P1 to P4.

From the secondary analysis based on IOPS-MS data, the subset of NP-BTcP cases for non-gender-specific cancer (Non-GSC) was considered ( $n = 1871$ ). Patients not in BTcP therapy, with diagnosis of multiple tumors or with rare tumors, and Non-GSC patients in hormone therapy were excluded from the analysis ( $n = 304$ ).

## Statistical Analysis

An univariable analysis was performed to compare gender within the population with NP-BTcP. Statistical tests for comparing means (Wilcoxon rank-sum test) and distributions (Chi-square and Fisher-exact tests) were performed to observe the main differences between males and females. A multivariable analysis according to metastatic status was performed to compare gender within the population with unpredictable pain, in particular, adjusted logistic multivariable models were implemented to assess associations between gender and selected variables. Odds ratios (ORs) and test results were reported with a 95% confidence level for significance. Analyses were computed with R software version 4.2.1.

## Results

The gender-based differences and sample characteristics of patients with BTcP are shown in Table 1. Male patients experienced BTcP more frequently in the thorax and less frequently in the abdomen compared to female patients (15% vs 11% and 21% vs 28%, respectively,  $p = 0.03$ ). Male patients also had a higher onset of BTcP (33% vs 28%,  $p = 0.04$ ) and

**Table 1** Non-GSC Cancer Patients: Main Characteristics by Gender (Male vs Female)

Characteristic	Female N = 584 <sup>a</sup>	Male N = 983 <sup>a</sup>	p-value <sup>b</sup>
<b>Age (years)</b>			0.610
N	584	983	
Mean (SD)	64 (12)	64 (12)	
Median (IQR)	64 (56, 73)	66 (57, 73)	
<b>Class of age</b>			0.839
≤55y	138 (24%)	220 (22%)	
56–70y	257 (44%)	439 (45%)	
>70y	188 (32%)	324 (33%)	
(Missing)	1	0	
<b>Primary cancer site<sup>c</sup></b>			<0.001
Gastrointestinal	178 (30%)	232 (24%)	
Haematological	17 (2.9%)	21 (2.1%)	
Head-Neck	20 (3.4%)	60 (6.1%)	
Liver	22 (3.8%)	36 (3.7%)	
Lung	183 (31%)	388 (39%)	
Melanoma	12 (2.1%)	18 (1.8%)	
Pancreas	106 (18%)	112 (11%)	
Sarcoma	10 (1.7%)	16 (1.6%)	
Thyroid	1 (0.2%)	3 (0.3%)	
Urological	35 (6.0%)	97 (9.9%)	
<b>Metastasis</b>			0.779
No	91 (16%)	148 (15%)	
Yes	493 (84%)	835 (85%)	
<b>Cancer therapy</b>			0.138
Biologic therapy	36 (6.2%)	43 (4.4%)	
Chemotherapy	274 (47%)	459 (47%)	
Radiotherapy	43 (7.4%)	102 (10%)	
No therapy	163 (28%)	281 (29%)	
Other therapies	68 (12%)	98 (10.0%)	

(Continued)

Table 1 (Continued).

Characteristic	Female N = 584 <sup>a</sup>	Male N = 983 <sup>a</sup>	p-value <sup>b</sup>
<b>Number/day of BTcP</b>			0.197
1 per day	192 (33%)	278 (28%)	
2 per day	227 (39%)	413 (42%)	
3 per day	127 (22%)	236 (24%)	
4 per day	38 (6.5%)	56 (5.7%)	
<b>Intensity of BTcP (scale)</b>			0.748
N	584	983	
Mean (SD)	7.56 (1.20)	7.56 (1.19)	
Median (IQR)	8.00 (7.00, 8.00)	8.00 (7.00, 8.00)	
<b>Type of BTcP</b>			0.869
Nociceptive	165 (28%)	272 (28%)	
Neuropathic	36 (6.2%)	67 (6.8%)	
Both	383 (66%)	644 (66%)	
<b>Site of BTcP</b>			0.033
Abdomen	162 (28%)	210 (21%)	
Arms	38 (6.5%)	66 (6.7%)	
Head-neck	22 (3.8%)	43 (4.4%)	
Thorax	66 (11%)	152 (15%)	
More sites	219 (38%)	364 (37%)	
Other sites	77 (13%)	148 (15%)	
<b>Onset</b>			0.037
≤10mins	421 (72%)	659 (67%)	
>10mins	163 (28%)	324 (33%)	
<b>BTcP Interference to daily life</b>			0.773
None	1 (0.2%)	4 (0.4%)	
Low	76 (13%)	117 (12%)	
High	351 (61%)	582 (60%)	
Very high	152 (26%)	270 (28%)	
(Missing)	4	10	
<b>BTcP therapy dosage</b>			0.025
N	584	983	
Mean (SD)	186 (247)	201 (244)	
Median (IQR)	100 (20, 200)	100 (30, 200)	
<b>Adverse reactions</b>			0.138
None	262 (45%)	479 (49%)	
Some	322 (55%)	504 (51%)	
<b>Setting</b>			0.002
Hospital	238 (41%)	392 (40%)	
Clinic + DH	216 (37%)	433 (44%)	
Hospice + Domicile	130 (22%)	158 (16%)	
<b>Satisfaction</b>			0.335
Low	114 (20%)	212 (22%)	
High	470 (80%)	771 (78%)	
<b>Therapy BTcP</b>			0.327
OTFT	23 (3.9%)	40 (4.1%)	
FBT	76 (13%)	133 (14%)	
FBST	100 (17%)	179 (18%)	
FPNS	144 (25%)	275 (28%)	
INFS	4 (0.7%)	14 (1.4%)	
MCLeV	130 (22%)	190 (19%)	
Other	107 (18%)	152 (15%)	

(Continued)

Table 1 (Continued).

Characteristic	Female N = 584 <sup>a</sup>	Male N = 983 <sup>a</sup>	p-value <sup>b</sup>
<b>Phenotype</b>			0.814
P1	97 (17%)	151 (15%)	
P2	184 (32%)	330 (34%)	
P3	252 (43%)	414 (42%)	
P4	51 (8.7%)	88 (9.0%)	
<b>Karnofsky</b>			<b>0.026</b>
N	584	983	
Mean (SD)	49.2 (19.6)	46.9 (19.1)	
Median (IQR)	50.00 (30.0, 70.0)	50.0 (30.0, 60.0)	
<b>Ecog</b>			0.470
≤2	181 (31%)	322 (33%)	
>2	403 (69%)	661 (67%)	

**Notes:** <sup>a</sup>n (%). <sup>b</sup>Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's Exact Test for Count Data with simulated p-value; Fisher's exact test; Significant p-values are reported in bold. <sup>c</sup> Urological cancer does not include prostate cancer.

**Abbreviations:** BTcP, breakthrough cancer pain; OTFC, oral transmucosal fentanyl citrate; FBT, fentanyl buccal tablet; FBST, sublingual fentanyl; FPNS, fentanyl pectin nasal spray; INFS, intranasal fentanyl, MCLcV, morphine injectable intravenously.

a higher BTcP therapy dosage (mean: 201 vs 186,  $p = 0.02$ ). Males were more likely to receive treatment in a clinic or day hospital, while females were more likely to receive treatment in a hospice or home setting (44% vs 37%; 22% vs 16%, respectively,  $p = 0.002$ ). Additionally, male patients had a lower Karnofsky score (mean: 46.9 vs 49.2,  $p = 0.03$ ). Other BTcP main elements were not found statistically significant. Results described above were mostly confirmed in the

Table 2 Metastatic vs Non-Metastatic Tumors by Gender (Male vs Female) in Non-GSC Cancer Patients

Variable	Non-Metastatic, No-GSC			Metastatic, No-GSC		
	Female N = 91 <sup>a</sup>	Male N = 148 <sup>a</sup>	p-value <sup>b</sup>	Female N = 493 <sup>a</sup>	Male N = 835 <sup>a</sup>	p-value <sup>b</sup>
<b>Class of age</b>			0.553			0.701
≤55y	18 (20%)	28 (19%)		120 (24%)	192 (23%)	
56–70y	36 (40%)	69 (47%)		221 (45%)	370 (44%)	
>70y	37 (41%)	51 (34%)		151 (31%)	273 (33%)	
(Missing)				1	0	
<b>Primary cancer site<sup>c</sup></b>			0.094			<0.001
Gastrointestinal	12 (13%)	17 (11%)		166 (34%)	215 (26%)	
Haematological	7 (7.7%)	6 (4.1%)		10 (2.0%)	15 (1.8%)	
Head-Neck	11 (12%)	20 (14%)		9 (1.8%)	40 (4.8%)	
Liver	5 (5.5%)	10 (6.8%)		17 (3.4%)	26 (3.1%)	
Lung	29 (32%)	70 (47%)		154 (31%)	318 (38%)	
Melanoma	2 (2.2%)	0 (0%)		10 (2.0%)	18 (2.2%)	
Pancreas	17 (19%)	21 (14%)		89 (18%)	91 (11%)	
Sarcoma	2 (2.2%)	2 (1.4%)		8 (1.6%)	14 (1.7%)	
Thyroid	1 (1.1%)	0 (0%)		0 (0%)	3 (0.4%)	
Urological	5 (5.5%)	2 (1.4%)		30 (6.1%)	95 (11%)	
<b>Cancer therapy</b>			0.563			0.021
Biologic therapy	1 (1.1%)	2 (1.4%)		35 (7.1%)	41 (4.9%)	
Chemotherapy	28 (31%)	59 (40%)		246 (50%)	400 (48%)	
Radiotherapy	15 (16%)	16 (11%)		28 (5.7%)	86 (10%)	
No therapy	35 (38%)	53 (36%)		128 (26%)	228 (27%)	
Other therapies	12 (13%)	18 (12%)		56 (11%)	80 (9.6%)	

(Continued)

Table 2 (Continued).

Variable	Non-Metastatic, No-GSC			Metastatic, No-GSC		
	Female N = 91 <sup>a</sup>	Male N = 148 <sup>a</sup>	p-value <sup>b</sup>	Female N = 493 <sup>a</sup>	Male N = 835 <sup>a</sup>	p-value <sup>b</sup>
<b>Number/day of BTcP</b>			0.066			0.075
1 per day	17 (19%)	40 (27%)		175 (35%)	238 (29%)	
2 per day	39 (43%)	57 (39%)		188 (38%)	356 (43%)	
3 per day	26 (29%)	47 (32%)		101 (20%)	189 (23%)	
4 per day	9 (9.9%)	4 (2.7%)		29 (5.9%)	52 (6.2%)	
<b>Intensity of BTcP (scale)</b>			0.132			0.775
N	91	148		493	835	
Mean (SD)	7.67 (1.19)	7.45 (1.18)		7.54 (1.21)	7.57 (1.19)	
Median (IQR)	8.00 (7.00, 8.00)	7.00 (7.00, 8.00)		8.00 (7.00, 8.00)	8.00 (7.00, 8.00)	
<b>Type of BTcP</b>			0.916			0.777
Nociceptive	17 (19%)	28 (19%)		148 (30%)	244 (29%)	
Neuropathic	6 (6.6%)	8 (5.4%)		30 (6.1%)	59 (7.1%)	
Both	68 (75%)	112 (76%)		315 (64%)	532 (64%)	
<b>Site of BTcP</b>			0.701			0.010
Abdomen	20 (22%)	26 (18%)		142 (29%)	184 (22%)	
Arms	7 (7.7%)	8 (5.4%)		31 (6.3%)	58 (6.9%)	
Head-neck	6 (6.6%)	6 (4.1%)		16 (3.2%)	37 (4.4%)	
Thorax	24 (26%)	39 (26%)		42 (8.5%)	113 (14%)	
More sites	23 (25%)	47 (32%)		196 (40%)	317 (38%)	
Other sites	11 (12%)	22 (15%)		66 (13%)	126 (15%)	
<b>Onset</b>			>0.999			0.023
≤10mins	60 (66%)	98 (66%)		361 (73%)	561 (67%)	
>10mins	31 (34%)	50 (34%)		132 (27%)	274 (33%)	
<b>BTcP Interference to daily life</b>			0.509			0.660
None	0 (0%)	0 (0%)		1 (0.2%)	4 (0.5%)	
Low	8 (9.0%)	19 (13%)		68 (14%)	98 (12%)	
High	62 (70%)	92 (62%)		289 (59%)	490 (59%)	
Very high	19 (21%)	37 (25%)		133 (27%)	233 (28%)	
(Missing)	2	0		2	10	
<b>BTcP therapy dosage</b>			0.377			0.040
N	91	148		493	835	
Mean (SD)	193 (240)	212 (234)		185 (248)	199 (246)	
Median (IQR)	100 (56, 200)	100 (100, 300)		100 (20, 200)	100 (30, 200)	
<b>Adverse reactions</b>			0.589			0.060
None	56 (62%)	85 (57%)		206 (42%)	394 (47%)	
Some	35 (38%)	63 (43%)		287 (58%)	441 (53%)	
<b>Setting</b>			0.378			0.003
Hospital	23 (25%)	38 (26%)		215 (44%)	354 (42%)	
Clinic + DH	51 (56%)	92 (62%)		165 (33%)	341 (41%)	
Hospice + Domicile	17 (19%)	18 (12%)		113 (23%)	140 (17%)	
<b>Satisfaction</b>			0.631			0.206
Low	22 (24%)	31 (21%)		92 (19%)	181 (22%)	
High	69 (76%)	117 (79%)		401 (81%)	654 (78%)	
<b>Therapy BTcP</b>			0.152			0.450
Other	16 (18%)	17 (11%)		91 (18%)	135 (16%)	
OTFT	2 (2.2%)	10 (6.8%)		21 (4.3%)	30 (3.6%)	
FBT	10 (11%)	9 (6.1%)		66 (13%)	124 (15%)	
FBST	22 (24%)	27 (18%)		78 (16%)	152 (18%)	
FPNS	25 (27%)	58 (39%)		119 (24%)	217 (26%)	
INFS	1 (1.1%)	4 (2.7%)		3 (0.6%)	10 (1.2%)	
MCLeV	15 (16%)	23 (16%)		115 (23%)	167 (20%)	

(Continued)

**Table 2** (Continued).

Variable	Non-Metastatic, No-GSC			Metastatic, No-GSC		
	Female N = 91 <sup>a</sup>	Male N = 148 <sup>a</sup>	p-value <sup>b</sup>	Female N = 493 <sup>a</sup>	Male N = 835 <sup>a</sup>	p-value <sup>b</sup>
<b>Phenotype</b>			<b>0.020</b>			0.873
P1	13 (14%)	12 (8.1%)	0.736	84 (17%)	139 (17%)	<b>0.009</b>
P2	21 (23%)	61 (41%)		163 (33%)	269 (32%)	
P3	46 (51%)	66 (45%)		206 (42%)	348 (42%)	
P4	11 (12%)	9 (6.1%)		40 (8.1%)	79 (9.5%)	
<b>Karnofsky</b>			0.287			0.193
N	91	148		493	835	
Mean (SD)	42.6 (20.4)	43.3 (19.4)		50.4 (19.2)	47.5 (19.0)	
Median (IQR)	40.0 (30.0, 60.0)	40.0 (30.0, 60.0)		50.0 (30.0, 70.0)	50.0 (30.0, 60.0)	
<b>Ecog</b>						
≤2	44 (48%)	61 (41%)		137 (28%)	261 (31%)	
>2	47 (52%)	87 (59%)		356 (72%)	574 (69%)	

**Notes:** <sup>a</sup>n (%). <sup>b</sup>Fisher's Exact Test for Count Data with simulated p-value (based on 2000 replicates); Wilcoxon rank sum test; Fisher's Exact Test for Count Data; significant p-values are reported in bold. <sup>c</sup>Urological cancer does not include prostate cancer.

**Abbreviations:** BTcP, breakthrough cancer pain; OTFC, oral transmucosal fentanyl citrate; FBT, fentanyl buccal tablet; FBST, sublingual fentanyl; FPNS, fentanyl pectin nasal spray; INFS, intranasal fentanyl, MCLv, morphine injectable intravenously.

metastatic subgroup (Table 2, right): the abdomen region was the main BTcP site for females with metastasis, while thoracic pain was found as more common among male metastatic patients (29% vs 22%; 14% vs 8.5%, respectively;  $p = 0.01$ ); the peak onset time ( $\leq 10$  min vs  $> 10$  min) remained higher for metastatic males (33% vs 27%,  $p = 0.02$ ); BTcP therapy dosage was meanly lower for female (185 vs 199,  $p = 0.04$ ). Results in care setting were confirmed in metastatic patients ( $p = 0.003$ ) as males showed a lower Karnofsky score (mean: 47.5 vs 50.4,  $p = 0.009$ ). Among non-metastatic group, P2 was more characterized by males (41% vs 23%,  $p = 0.02$ ) while females were predominant among others. Although not reaching the significance ( $p = 0.06$ ), males were less prone to undergo any adverse reactions than females among metastatic cancer patients.

Finally, Table 3 shows logistic multivariable regression for gender stratified by metastatic status. In the non-metastatic subgroup, male cancer patients were more likely to be treated with OTFT (OR = 7.86, 95% CI = [1.34, 68.9]) and with FPNS (OR = 4.45, 95% CI = [1.45, 14.2]). Phenotype was associated with gender: male cancer patients were more likely to belong to P2 (OR = 3.05, 95% CI = [1.03, 9.23],  $p = 0.03$ ). Setting was found as barely associated with gender ( $p = 0.07$ ).

In Metastatic group, males were 35% less likely to be taken into care by hospice or domicile than females (OR = 0.65, 95% CI = [0.46, 0.91],  $p = 0.01$ ), were more prone to suffer from thorax BTcP (OR = 1.99, 95% CI = [1.30, 3.09]), underwent radiotherapy (OR = 2.31, 95% CI = [1.22, 4.42]) and experimented a higher onset (OR = 1.43, 95% CI = [1.10, 1.87]).

**Table 3** Logistic Regression Models for Gender (Male vs Female) and by Metastatic Status in Non-GSC Cancer Patients

Characteristic	Non-Metastatic, No-GSC			Metastatic, No-GSC		
	OR <sup>a</sup>	95% CI <sup>a</sup>	p-value <sup>b</sup>	OR <sup>a</sup>	95% CI <sup>a</sup>	p-value <sup>b</sup>
<b>Class of age</b>			0.950			0.397
≤55y	1	–	0.071	1	–	<b>0.014</b>
56–70y	0.97	0.42, 2.23		1.05	0.78, 1.41	
>70y	0.88	0.34, 2.19		1.24	0.89, 1.72	
<b>Setting</b>						
Hospital	1	–		1	–	
Clinic + DH	1.17	0.49, 2.79		1.11	0.84, 1.47	
Hospice + Domicile	0.35	0.12, 1.05		0.65	0.46, 0.91	

(Continued)

Table 3 (Continued).

Characteristic	Non-Metastatic, No-GSC			Metastatic, No-GSC		
	OR <sup>a</sup>	95% CI <sup>a</sup>	p-value <sup>b</sup>	OR <sup>a</sup>	95% CI <sup>a</sup>	p-value <sup>b</sup>
<b>Cancer therapy</b>			0.658			<b>0.035</b>
Biologic therapy	1	–		1	–	
Chemotherapy	1.95	0.06, 41.5		1.17	0.71, 1.92	
Radiotherapy	1.21	0.04, 26.8		2.31	1.22, 4.42	
No therapy	1.27	0.04, 26.6		1.30	0.76, 2.19	
Other therapies	0.97	0.03, 21.5		1.07	0.59, 1.93	
<b>Site of BTcP</b>			0.262			<b>0.033</b>
Abdomen	1	–		1	–	
Arms	0.86	0.21, 3.40		1.42	0.86, 2.38	
Head-neck	1.02	0.23, 4.46		1.66	0.88, 3.22	
Thorax	1.48	0.53, 4.15		1.99	1.30, 3.09	
More sites	2.24	0.92, 5.55		1.20	0.89, 1.61	
Other sites	2.80	0.96, 8.65		1.41	0.96, 2.08	
<b>Onset</b>			0.425			<b>0.007</b>
≤10mins	1	–		1	–	
>10mins	0.74	0.35, 1.54		1.43	1.10, 1.87	
<b>BTcP Interference to daily life</b>			0.542			0.371
None	(NA)			1	–	
Low	1	–		0.22	0.01, 1.76	
High	0.55	0.17, 1.67		0.28	0.01, 2.15	
Very high	0.69	0.18, 2.41		0.30	0.01, 2.28	
<b>Therapy BTcP</b>			<b>0.047</b>			0.218
Other	1	–		1	–	
OTFT	7.86	1.34, 68.9		0.96	0.51, 1.84	
FBT	1.21	0.31, 4.77		1.42	0.92, 2.20	
FBST	1.69	0.55, 5.25		1.38	0.92, 2.07	
FPNS	4.45	1.45, 14.2		1.48	1.01, 2.17	
INFS	1.95	0.18, 48.3		3.38	0.96, 15.8	
MCLeV	1.79	0.50, 6.53		1.19	0.78, 1.81	
<b>BTcP therapy dosage</b>	1.00	1.00, 1.00	0.395	1.00	1.00, 1.00	0.384
<b>Adverse reactions</b>			0.073			0.375
None	1	–		1	–	
Some	1.93	0.94, 4.08		0.89	0.69, 1.15	
<b>Satisfaction</b>			0.348			0.233
Low	1	–		1	–	
High	1.47	0.65, 3.32		0.83	0.61, 1.12	
<b>Phenotype</b>			<b>0.029</b>			0.536
P1	1	–		1	–	
P2	3.05	1.03, 9.23		0.80	0.56, 1.15	
P3	1.20	0.40, 3.64		0.76	0.52, 1.11	
P4	0.84	0.21, 3.39		0.85	0.51, 1.43	
<b>Ecog</b>			0.091			0.265
≤2	1	–		1	–	
>2	2.05	0.89, 4.85		0.85	0.63, 1.13	

**Notes:** <sup>a</sup>OR = Odds Ratio (Female = reference group), CI = Confidence Interval. <sup>b</sup>Wald test; significant p-values are reported in bold.

**Abbreviations:** BTcP, breakthrough cancer pain; OTFC, oral transmucosal fentanyl citrate; FBT, fentanyl buccal tablet; FBST, sublingual fentanyl; FPNS, fentanyl pectin nasal spray; INFS, intranasal fentanyl; MCLeV, morphine injectable intravenously.

## Discussion

BTcP represents a clinical peculiarity of cancer pain characterized by distinct pathogenic mechanisms underlying its subtypes.<sup>13–20</sup> Given the complexity of the NP-BTcP subtype, it is crucial to enhance its characterization for more effective therapy guidance, to ameliorate patients' quality of life and satisfaction.<sup>7,19,20</sup> To our knowledge, this is the first study that investigates gender differences in the NP-BTcP phenomenon.

Regarding our results, we found that female patients showed more frequent BTcP in the abdomen region and less in the thorax compared to male patients; moreover, male patients also had a higher onset of BTcP and BTcP therapy dosage. Additionally, female patients had a higher Karnofsky score. Such findings were confirmed among metastatic group where abdomen BTcP site was more frequent for females and the thorax region occurred more frequently among males; moreover, the peak onset remained lower for females such as the BTcP therapy dosage, among the metastatic group, too.

The multivariable analysis demonstrates that P2 was mainly characterized by non-metastatic male patients, while the other phenotypes were greater for non-metastatic females. The role of a phenotype characterization of BTcP needs to be further investigated for a possible useful function in the management of cancer-related pain in patients with non-metastatic disease, taking into account gender differences and other key variables. Moreover, as reported by previous analyses,<sup>7,18,20</sup> several key points should be considered in the pharmacological management of BTcP to improve patients' quality of life.

## Conclusion

Our analysis sheds light on gender differences in the NP-BTcP phenomenon, particularly in its intensity, onset and treatment profile. Female patients exhibited distinct patterns, experiencing more frequent BTcP in the abdomen region, with a shorter onset and lower BTcP therapy dosage compared to male patients. Moreover, females tended to have a higher Karnofsky score, indicating potentially better functional status. These findings were consistent across both non-metastatic and metastatic subgroups, underscoring the relevance of gender-specific considerations in pain management strategies. Additionally, the analysis of BTcP phenotypes revealed differential distributions between genders. Consequently, there is a need for further investigation into the role of phenotype characterization in guiding personalized pain management approaches, especially for non-metastatic patients. Recognizing and addressing gender disparities in NP-BTcP can contribute to more effective and tailored interventions, ultimately improving the quality of life for individuals suffering from cancer-related pain.

## Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (PROTOCOLLO DI STUDIO IOPS-MS) Policlinico Tor Vergata (REGISTRO SPERIMENTAZIONI n.21/13) Roma, 20 February 2013.

## Data Sharing Statement

All data are available in the manuscript and at link DOI: "10.5281/zenodo.7821879".

## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patient(s) to publish this paper.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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