Published in final edited form as:

Semin Oncol Nurs. 2019 June ; 35(3): 291–299. doi:10.1016/j.soncn.2019.04.011.

Genetic Variants Associated with Cancer Pain and Response to Opioid Analgesics: Implications for Precision Pain Management

Gee Su Yang, PhD, RN^a, Natalie M. Barnes^a, Debra E. Lyon, PhD, RN, FAAN^a, Susan G. Dorsey, PhD, RN, FAAN^b

^aUniversity of Florida College of Nursing, Gainesville, FL

^bUniversity of Maryland School of Nursing, Department of Pain and Translational Symptom Science, Baltimore, MD

Abstract

Objective: To review the current knowledge on the association of genetic variants with cancer pain.

Data Sources: Data-based publications and review articles retrieved from PubMed, CINAHL, and Web of Science, as well as an additional search in Google Scholar.

Conclusion: Genetic variability can influence differential pain perception and response to opioids in cancer patients, which will have implications in the optimal personalized treatment of cancer pain. More studies are warranted to replicate findings.

Implications for Nursing Practice: Nurses are poised to educate patients on biomarker testing and interpretation and to use precision pain management strategies based on this information.

Keywords

genetic variant; genetic polymorphism; biomarker; cancer; pain; precision medicine

Introduction

Cancer is a common source of the development of chronic pain, resulting in a decrease in quality of life, functional status, and productivity, as well as an increase in morbidity, mortality, and societal cost of pain treatment.¹ As the number of cancer survivors rapidly grows over time (18 million in 2020) in the U.S.,² management and prevention of cancer pain have been considered a significant public health challenge at individual and population levels.¹ A recent meta-analysis of 122 studies on cancer-related pain found that more than 66% of patients with advanced and metastatic cancers and 55% of patients undergoing

Address correspondence to: Gee Su Yang, PhD, RN, University of Florida, College of Nursing, 1225 Center Drive, Gainesville, FL 32610; or Susan G. Dorsey, PhD, RN, FAAN, University of Maryland, School of Nursing, 655 W. Lombard St., Baltimore, MD 21201. gyang1@ufl.edu (G.S. Yang) or sdorsey@umaryland.edu (S.G. Dorsey).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

anticancer treatment reported pain.³ Furthermore, 30% of people with cancer overall experienced chronic daily pain, of whom 48% considering the tumor itself a source of pain, and 24% reporting that their cancer pain is because of treatment.⁴ Given that cancer pain can arise from multiple sources (eg, pressure of tumors on adjacent tissues, direct damage to the peripheral and central nervous system, stimulation on somatic nociceptive or visceral nociceptors, chemotherapy, radiotherapy, and/or surgery), either directly or indirectly, and cancer patients are more likely to be older and have more comorbidities, which in themselves are associated with pain,^{1,5,6} difficulty exists in clearly understanding the etiologies of cancer pain. In addition, the multiple and sometimes inter-related phenotypes of cancer pain (pain during active treatment, survivorship, and palliative care) may have distinct genetic variants. Therefore, there are still many questions related to the genetic contributors to cancer-related pain.

Currently, a growing body of literature reporting the results of human genetic association studies have suggested that genetic variability, alone or in interaction with environmental factors, can contribute to differential pain phenotypes and analgesic response.^{7,8} It is well recognized that genetic factors influence the modulation of pain in the central and peripheral nervous system.⁹ They can alter the transmission of nociception or central inhibitory signals, affecting individual susceptibility to pain and response to analgesic drugs.^{1,9,10} For example, single nucleotide polymorphisms (SNPs), commonly examined in genetic association studies as a stable biomarker,¹¹ are involved in increasing or decreasing a risk of pain. In the case of coding SNPs, which can change the amino acid sequence of the gene's protein product, the result could be alterations in the expression level of an important protein.⁸ With the rapid advancement of biotechnology platforms and powerful computational analysis for explaining underlying genetic mechanisms,¹² genes associated with cancer pain can be targeted for developing effective screening approaches and therapeutic strategies that are individualized in the era of personalized medicine,¹ referring to "prevention and treatment strategies that take individual variability into account."^{13(p.793)} Here, this review is focused on discussing the current knowledge on genetic variability that may play a potential role in differential pain perception and response to opioid analgesics in the treatment of cancer pain.

Search Strategies and Information Sources

We searched data-based publications and review articles with regard to genetic variants that have been implicated in cancer pain. The articles were retrieved from PubMed, CINAHL, and Web of Science; an additional search was conducted in Google Scholar. Genetic association studies on cancer pain phenotype were selected to narrow down the scope of this review. Candidate genetic polymorphisms that were reported to have a significant association with pain in cancer patients were included. The information on gene, SNP rsID, nucleotide change, gene pathway/function (eg, inflammation, neurotransmission, and drug transport and metabolism), associated pain phenotype, type of cancer, and references is presented. Genetic polymorphisms associated with cancer pain were divided into "cancer (itself) pain" and "post-cancer treatment pain" based on the International Association for the Study of Pain classification of chronic pain for the *International Classification of Diseases* (ICD) (Tables 1 and 2).¹⁴ According to the International Association for the Study of Pain definition and general structure of chronic cancer-related pain, cancer-related pain is

classified as “cancer pain” resulting from the primary cancer or metastases (eg, visceral cancer pain, bone cancer pain, and neuropathic cancer pain) and “post-cancer treatment pain” related to surgery (post-cancer surgery pain; pain resulting from tissue injury during operations, eg, stretching and retracting, or with the postsurgical progression), chemotherapy (post-cancer medicine pain), and radiotherapy (postradiotherapy pain).¹⁴ In addition, the information on genetic polymorphisms associated with response to opioid is described (Table 3). Table 4 provides glossary terms frequently used in this review.

Genetic Variants Associated with Cancer Pain

Associations between genetic polymorphisms and cancer pain before the initiation of anticancer treatments have been described in several studies as shown in Table 1.^{5,11,15–21} A majority of genes are involved in the inflammatory pathway. It is well documented that chronic inflammation promotes tumor growth and dissemination in patients with cancer, and cancer itself contributes to the release of inflammatory molecules, such as chemokines and cytokines, resulting in the sensitization of sensory nerve terminals.^{18,22,23} Prior reports have indicated that SNPs involved in the inflammation pathway indirectly regulate cytokine serum expression levels, which may have an impact on individual pain variability and immune functioning.^{24–26}

Lung cancer

Reyes-Gibby and colleagues noted that polymorphisms in the interleukin 8 (*IL-8*), nuclear factor kappa-B inhibitor alpha (*NFKBIA*), tumor necrosis factor-alpha (*TNF-α*), and prostaglandin-endoperoxide synthase 2 (*PTGS2*) genes have been suggested as candidates for predicting cancer pain in patients with lung cancer.^{5,18,19} White patients homozygous for the minor allele at *IL-8* –251T>A and *TNF-α* –308G>A (rs1800629) showed 2.35 and 1.67 times higher risk for pain compared with those homozygous for the major allele, respectively, in which pain was measured by the Brief Pain Inventory (n = 446).^{5,18} The polymorphisms are reported to affect gene expression, which may cause higher serum levels of IL-8 and TNF-α.²⁷ On the contrary, non-Hispanic white cancer patients homozygous for the minor allele at *PTGS2* rs5275 (odds ratio [OR] = 0.33, 95% confidence interval [CI], 0.11 to 0.97) and at *NFKBIA* exon+50C>T (rs8904) (OR = 0.64, 95% CI, 0.43 to 0.93) exhibited a reduced risk for pain (n = 667). (In the paper by Reyes-Gibby et al, “an additive model for *NFKBIA* Ex6 +50C>T (rs8904) was predictive of severe pain.”)¹⁸

Rausch and colleagues^{16,17} studied the association of SNPs in cytokine genes with pain severity in white lung cancer survivors (n = 1,149). The *IL-10* SNP (rs1800871) was a significant predictive factor for pain severity in early survivors (<3 years since diagnosis; OR = 0.97–0.99) and middle-term survivors (3 to 5 years since diagnosis; OR = 0.94–0.99).¹⁶ Patients possessing at least one minor allele at rs1799964 in the lymphotoxin alpha (*LTA*) gene, a member of the TNF family playing a central role in inflammation, showed a protective effect for pain (lower pain scores on the medical outcomes study short-form general health survey [SF-8]) while those possessing at least one minor allele at rs5277 in the *PTGS2* gene, encoding the cyclooxygenase 2 (COX2) enzyme, had a higher risk for developing pain.¹⁷

Pancreatic cancer

In a study by Reyes-Gibby et al,¹¹ 484 patients who were newly diagnosed with pancreatic cancer were evaluated on the association of cytokine gene polymorphisms with pain severity. The pain score was rated on a 0–10 numeric scale, with the higher score indicating the severe pain. Among *IL-1β*, *IL-6*, *IL-8*, *IL-10*, *IL-18*, *TNF-α* and *NF-κB* SNPs, the *IL-8* SNP (–251T>A) was significantly associated with a risk for pain in patients with pancreatic cancer. Patients with the TT or TA genotype were two times more likely to experience severe pain compared with those with the AA genotype (OR = 2.43, 95% CI, 1.3 to 4.7).

Breast cancer

In a study by McCann et al,¹⁵ polymorphisms in interleukin 1 receptor 1 (*IL1RI*) and *IL-13* genes appeared to play a role in modifying individual pain perception. In women prior to breast cancer surgery (n = 398), carriers with the CT or TT genotype for the *IL1RI* rs2110726 were at a lower risk for pain compared with those with the CC genotype. On the contrary, carriers with the GA or AA genotype for a SNP in *IL-13* (rs1295686) had a 57% increased risk of reporting breast pain before surgery.¹⁵ Cajanus et al²¹ have indicated that SNPs in the *FAAH* gene, which is involved in the metabolism of the endocannabinoid anandamide, played a role in endogenous analgesia (inhibition of the activity of FAAH promotes endocannabinoid-mediated analgesic effects)²⁸ and exhibited a significant association with experimental cold pain sensitivity in female Finnish patients with breast cancer before breast-conserving surgery or mastectomy (n = 900). Patients homozygous for the minor allele at rs3766246, rs324420 (Pro129Thr), rs4660928, and rs1571138 in the *FAAH* gene exhibited significantly lower cold pain sensitivity compared with those homozygous or heterozygous for major allele of these polymorphisms?²¹

Other

Polymorphisms in catechol-O-methyltransferase (*COMT*) and opioid receptor mu (μ) 1 (*OPRM1*) genes were associated with the preoperative pain sensitivity in cancer patients. The *COMT* gene encodes an enzyme that inactivates catechols, such as dopamine, noradrenaline, and adrenaline,²⁹ and the *OPRM1* gene encodes the receptor of opioid, of which polymorphisms may modulate the efficacy of opioid analgesics in cancer pain.³⁰ Chinese patients with two copies of the minor allele at *COMT* Val158Met (ie, a substitution of methionine [Met] for valine [Val] at codon 158) and *OPRM1* 118A>G loci were reported to have higher pain sensitivity before cancer surgery (n = 300).²⁰

Genetic Variants Associated with Post-cancer Treatment Pain

Many studies have found associations between post-cancer treatment pain and genetic polymorphisms. The influence of genetic polymorphisms on post-cancer surgery pain and post-cancer medicine pain has been largely evaluated on breast cancer, as shown in Table 2. Some genes associated with post-cancer treatment pain seem to be involved in the drug metabolism and transport pathway. Polymorphisms of those genes may change pharmacokinetics of drugs in terms of drug efficacy and safety, and interact with molecules related to pain-transporting analgesics.^{10,31}

Breast cancer

Post-cancer surgery pain.—Stephens and colleagues^{32,33} found that polymorphisms in inflammatory pathway genes, such as interleukin 1 receptor type 2 (*IL1R2*), *IL-6*, *IL-10*, C-X-C motif chemokine ligand 8 (*CXCL8*), and *TNF*, have been associated with persistent pain following mastectomy or lumpectomy in patients with breast cancer (n = 398). Postoperative pain was assessed monthly using the breast symptoms questionnaire, postsurgical pain questionnaire, and Numerical Rating Scale through the 6-month follow-up point. Patients homozygous for the minor allele at rs11674595 in the *IL1R2* gene were demonstrated to have a substantially increased risk for severe pain compared with those homozygous or heterozygous for the major allele at the SNP locus (OR = 36.1, 95% CI, 2.02 to 643.37).³² On the contrary, patients who possess *IL-10* haplotype A8, consisting of seven SNPs (ie, rs3024505, rs3024498, rs3024496, rs1878672, rs1518111, rs1518110, and rs3024491), showed a decreased risk for severe breast pain by 79% per each dose of this haplotype.³² Notably, patients homozygous for the minor allele in *IL-6* rs2069840, *CXCL8* rs4073, and *TNF* rs1800610 were less likely to develop pain compared with those homozygous or heterozygous for the major allele in these genes, as much as 79%, 60%, and 63%, respectively.³³

SNPs in the *COMT* gene may contribute to the variability in pain sensitivity and severity following breast cancer surgery. In a study by Fernández-de-las Peñas et al,³⁴ patients who received a simple mastectomy or quadrantectomy (n = 128, Spain) were assessed using the visual analogue scale and experimental pain tests (pressure pain thresholds in the neck and shoulder areas). It was observed that patients with Met/Met genotype (rs4680) had greater neck pain and lower pressure pain threshold than those with Val/Met or Val/Val genotype. Kambur et al³⁵ also determined the influence of *COMT* polymorphisms on experimental and acute pain in female Finnish patients with breast cancer undergoing surgery (n = 1,000). In this study, polymorphisms within the *COMT* gene (rs165774 and rs887200) were significantly correlated with heat pain (+48 °C) and cold pain (+2–4 °C), respectively.

Notably, persistent postmastectomy pain appears to be associated with SNPs in calcium and potassium channel genes. In 482 white women, the presence of a 3-SNP haplotype (A-C-C) (rs4820242, rs2284015, and rs2284017) in the voltage-dependent calcium channel gamma subunit 2 (*CACNG2*) gene significantly increased a risk of developing chronic mastectomy pain measured by the Brief Pain Inventory and Numerical Rating Scale at 38 months after surgery.³⁶ Langford et al³⁷ indicated that specific SNPs in potassium channel genes, which are involved in the modulation of neuronal excitability, may be susceptible to postsurgical breast pain. As for mild pain, patients who possess the minor allele for a SNP in the potassium voltage-gated channel subfamily A member 1 (*KCNA1*) (rs4766311), potassium inwardly rectifying channel subfamily J member 3 (*KCNJ3*) (rs12995382), or potassium channel subfamily K member 9 (*KCNK9*) (rs2542424) remained significantly associated with a reduced risk of developing pain. On the contrary, patients who possess one or two copies of the minor allele for a SNP in the potassium voltage-gated channel subfamily D member 2 (*KCND2*) (rs1072198), *KCNJ3* (rs17641121), *KCNJ6* (rs858003), or *KCNK9* (rs2545457) had a 2.3-, 8.5-, 10.0-, or 2.2-fold higher risk of developing pain, respectively. As for severe pain, patients heterozygous or homozygous for the minor allele at rs17376373

in the *KCND2* gene had an 88% lower risk for pain, and patients having *KCNJ3* haplotype A2 (rs3111020 and rs11895478) were reported to show an 89% decrease per each dose of this haplotype. On the contrary, patients with one or two copies in *KCNJ6* rs2835925 and *KCNK9* rs2014712 showed a significantly increased risk of developing pain.

Post-cancer medicine pain.—Chemotherapy treatment may cause differential individual susceptibility to pain. It is well documented that one of the major adverse effects in the treatment with third-generation aromatase inhibitors (AIs), such as anastrozole, letrozole, and exemetane, is musculoskeletal pain. Nearly 50% of patients with breast cancer receiving AIs report joint pain and stiffness, and 20% to 30% discontinue the medication, which may increase cancer recurrence rate and mortality.^{38–40} In a prospective cohort study on the association between SNPs and AI-associated arthralgia (n = 334, Spain),⁴¹ SNPs in genes related to the metabolism of estrogens and vitamin D (eg, cytochrome P450 family 17 subfamily A member 1 [*CYP17A1*], cytochrome P450 family 27 subfamily B member 1 [*CYP27B1*], vitamin D receptor [*VDR*], and osteoprotegerin [*OPG*]) appeared to predict the risk of AI-associated arthralgia. Seven SNPs (rs4919687, rs4919683, rs4919687, rs3781287, rs10786712, rs6163, and rs743572) in the *CYP17A1* gene were significantly associated with pain severity. In the multivariate analysis, β coefficients of each polymorphism were -0.60 ($P = .015$) for rs4919687, -0.67 ($P = .003$) for rs4919683, -0.71 ($P = .003$) for rs4919687, -0.63 ($P = .004$) for rs3781287, -0.66 ($P = .003$) for rs10786712, -0.65 ($P = .003$) for rs6163, and -0.62 ($P = .005$) for rs743572, indicating that these *CYP17A1* polymorphisms were significantly associated with lower pain increase. In addition, a significant association was observed between visual analogue scale increase and polymorphisms in *CYP27B1* (rs4646536) and *VDR* (rs11568820). Notably, the polymorphism at rs2073618 in the *OPG* gene, known as TNF receptor superfamily member 11B (*TNFRSF11B*), was also significantly associated with pain severity in which patients with the CG or GG genotype experienced more pain (visual analogue scale) compared with those with the CC genotype.⁴²

Two *COMT* polymorphisms, including rs4680 and rs4818, are also known to contribute to pain severity after surgery and chemotherapy in patients with breast cancer (n = 51).⁴³ Patients with the AA genotype in *COMT* rs4680 exhibited increased pain-related interference, and patients with the GG genotype in *COMT* rs4818 showed decreased pain severity and interference after surgery and chemotherapy treatment.

Bone metastases

Postradiotherapy pain.—Genetic polymorphisms have been associated with postradiotherapy pain in cancer in several studies.^{44,45} In patients with bone metastases undergoing palliative radiotherapy, whose primary cancer sites were breast, lung, and prostate (n = 52), nine polymorphisms across the aquaporin 7 (*AQP7*), plasminogen activator urokinase receptor (*PLAUR*), and ElaC ribonuclease Z 2 (*ELAC2*) genes may be associated with pain. Especially, rs7668797 in the *AQP7* gene, rs4760 A>G in the *PLAUR* gene, and rs1154302 T>C in the *ELAC2* gene, were the most significant polymorphisms in predicting postradiotherapy pain.⁴⁴ In patients with differentiated thyroid cancer undergoing ¹³¹I radiotherapy (n = 203),⁴⁵ patients heterozygous for the minor allele for the *TNF- α* rs1800629 were more likely to report pain in the neck area compared with those

homozygous for the major allele. In addition, SNPs in ataxia-telangiectasia mutated (*ATM*) rs11212570, *NF-κB* rs230493, and transforming growth factor (*TGF-β*) rs1800469 and rs2241716 may contribute to individual susceptibility in throat pain at 6 weeks post-radiotherapy.⁴⁵

Multiple Types of Cancer

Post-cancer surgery pain.—Recently, the association between polymorphisms in the purinergic P2Y₁₂ receptor (*P2RY12*), a site where microglial chemotaxis is induced in the nervous system, and pain severity were investigated in Japanese cancer patients who reported pain (n = 355). Five SNPs (rs3732765, rs9859538, rs17283010, rs11713504, and rs10935840) of the *P2RY12* gene were demonstrated to have a significant association with cancer pain and postoperative pain severity. Patients homozygous for the minor allele of these SNPs reported greater pain compared with those homozygous for the major allele or heterozygous for the minor alleles.⁴⁶

Genetic Variants Associated with Response to Opioid Treatment

Cancer patients need adequate treatment for controlling pain because unrelieved pain may affect disease outcomes and may likely develop into chronic persistent pain.⁴⁷ Opioids are currently used as the most effective treatment as first-line therapy for cancer pain.^{48–50} Opioids bind to receptors in mu (μ), kappa (κ), or delta (δ) subtypes in the central nervous system, producing signaling.⁵¹ Once opioids bind to their G-protein coupled receptors, neuronal cell membranes are hyperpolarized and neurotransmitter release is reduced, leading to an analgesic effect.^{51–53} The majority of opioid analgesics are the mu agonist,⁵⁰ which are divided into a couple of classes depending on the extent to which they interact with their receptors. The pure mu agonist opioids, which are commonly used for managing patients who are not chronically taking opioid drugs (ie, opioid naïve) or restricted in exposure to opioids, include morphine, hydromorphone, oxycodone, hydrocodone, codeine, fentanyl, and methadone.⁵⁰ Buprenorphine is an example of partial agonists, which are used for treating opioid addiction, and tramadol and tapentadol depend on both mu agonism and monoaminergic mechanism.⁵⁰ In addition, the response to these opioids is associated with their metabolism in relation to the cytochrome P450 (CYP) enzymes, which may alter opioid formation and its concentration in circulation.^{51,54} For example, increased CYP2D6 activity is observed in “extensive metabolizers” and “ultra-rapid metabolizers.”⁵⁴ Some cancer patients suffer from undertreated pain because of a poor response to opioid analgesics. Genetic biomarkers may help increase an understanding of the differential sensitivity to the opioids (eg, tolerance and consumption) to prevent inadequate cancer pain management.⁵⁴ To date, studies on the genetic influence on the analgesic effects and efficacy of opioid treatment have primarily considered *OPRM1*, *COMT*, and ATP binding cassette subfamily B member 1 (*ABCB1*) genes.

Recently, a meta-analysis including 12 studies (n = 2,118) has indicated that the *OPRM1* 118A>G polymorphism (rs1799971) may affect variability in the opioid analgesic effect in cancer patients.⁵⁵ Patients homozygous or heterozygous for the minor allele in *OPRM1* 118A>G (rs1799971) are reported to require more opioids to relieve pain than those

homozygous for the major allele (standardized mean difference = -0.3 , 95% CI, -0.45 to -0.15). For example, it was reported that Chinese cancer patients ($n = 112$) with the AG, GG, and AA genotypes needed 97.33 ± 69.07 mg/24 hours, 152.34 ± 83.13 mg/24 hours, and 72.48 ± 64.05 mg/24 hours of opioids, respectively, indicating that opioid consumption of patients homozygous for the major allele was significantly lower than that of those with at least one minor allele.⁵⁶ In another study by Cajanus et al,⁵⁷ women with the GG genotype consumed the highest amount of oxycodone (0.16 mg/kg); however, women with the AA genotype needed the lowest amount of oxycodone (0.12 mg/kg) after breast cancer surgery ($P = .003$). Similarly, in the study of Hajj et al,⁵⁸ the AG genotype of *OPRM1* rs1799971 required a higher dose of morphine at 24 hours to achieve adequate analgesic efficacy compared with the AA genotype (AG genotype = 51.37 ± 46.35 mg, AA genotype = 29.97 ± 26.96 mg; $P = .01$) in 89 patients with multiple types of cancer (eg, breast, gastrointestinal tract, lung, hematology, gynecology, and others).

The *COMT* SNP (rs4680; Val158Met) has been also shown to influence the efficacy of opioids in patients with cancer pain. Carriers with the Val/Val genotype required a higher dose of morphine (155 ± 160 mg/24 hours; $n = 44$) than carriers with the Val/Met (117 ± 100 mg/24 hours; $n = 96$) and Met/Met genotype (95 ± 99 mg/24 hours; $n = 67$) ($P = .025$).⁵⁹ Matsuoka et al⁶⁰ have suggested that 50 opioid-naïve patients with Val/Val, Val/Met, and Met/Met genotypes required 35.2 ± 11.5 mg, 29.5 ± 2.3 mg, and 25.0 ± 7.1 mg of morphine, respectively, in which the presence of the Val/Val genotype contributed to the higher dose of morphine requirement for cancer pain relief compared with the presence of Val/Met and Met/Met genotypes ($P = .013$).

The polymorphism of the *ABCB1* gene (3435C>T), encoding the efflux transporter P-glycoprotein, may explain interindividual differences in the response to opioids. Cancer patients homozygous for the minor allele showed greater pain relief by morphine therapy than those homozygous for the major allele ($n = 137$).⁶¹ The Numerical Rating Scale pain scores in patients with the TT genotype and the CC genotype were decreased by 4.39 ± 2.21 and 2.31 ± 1.73 , respectively, following morphine treatment. However, the pain relief effect by morphine was not significantly different between patients with the TC genotype and those with the CC genotype.⁶¹ Similarly, the potential relationship of the polymorphism in *ABCB1* (3435C>T) with opioid requirement was demonstrated in Chinese patients with cancer pain ($n = 112$). Patients homozygous for the minor T allele were less likely to require a lower dose of opioids at 24-hour compared with those with at least one major C allele (TT genotype = 66.04 ± 52.57 mg/kg; CT genotype = 103.87 ± 71.38 mg/kg; CC genotype = 100.43 ± 82.24 mg/kg).⁵⁶

In addition to those genes, *IL-6*, guanosine triphosphate (*GTP*), cyclohydrolase 1 (*GCHI*), and TAO kinase 3 (*TAOK3*) genes may explain variability in the efficacy of opioids in cancer patients with pain. In a study by Reyes-Gibby et al,⁶² lung cancer patients with GC and GG genotypes of *IL-6* -174G>C required 73.17 mg/24 hours and 69.61 mg/24 hours, respectively; however, those with the CC genotype received 181.67 mg/24 hours, indicating that the dose of opioids of the CC genotype was 4.7 times higher than that of GC and GG genotypes to achieve the equivalent pain relief ($n = 140$). Furthermore, the *GCHI* haplotype, consisting of three SNPs (rs8007267, rs3783641, and rs10483639) may affect the initiation

time of opioid therapy after cancer diagnosis.⁶³ The *GCHI* gene is known to encode the enzyme protein that catalyzes the formation from GTP to tetrahydrobiopterin (BH4).⁶³ In a mouse animal model, reduced BH4 expression has shown a protective effect against pain.⁶⁴ Patients homozygous for the genetic variants were shown to initiate morphine treatment at 78 ± 65.2 months after their cancer diagnosis, while those heterozygous for the genetic variants or non-carriers started the treatment at 37 ± 46.5 months and 30.4 ± 43.8 months after the diagnosis, respectively, suggesting that *GCHI* variants may result in decreased BH4, postponing the development of cancer pain ($n = 251$).⁶³ In addition, polymorphisms in the *TAOK3* gene, encoding serine/threonine-protein kinase, were significantly associated with the amount of opioid used for cancer pain. Patients homozygous for the minor allele in *TAOK3* rs796484 (G>A) and rs1277441 (T>C) had higher opioid requirements in patients with cancer pain ($n = 110$).⁶⁵ However, negative evidence also exists on the association of genetic variability with opioid use in the treatment of cancer pain. In a European genetic association study ($n = 2,294$), cancer patients treated with morphine, oxycodone, fentanyl, or others did not show any associations between opioid dose and 112 SNPs across the 25 genes, including *OPRM1*, *COMT*, and *ABCB1*.³¹

Implications for Nursing Practice and Research

This review summarizes the current knowledge on genetic polymorphisms that have been implicated in cancer pain, post-cancer treatment and surgical pain, and response to opioid analgesics. Most genetic association studies published to date have been focused on cancer pain in non-Hispanic white patients with solid tumors (eg, breast cancer, lung cancer), indicating that more research is warranted to elucidate the influence of genetic variability on pain in patients experiencing other types of cancers (eg, hematologic cancer, head and neck cancer) and patients with diverse ethnic/racial background, including African American, Hispanic, and Asian. Although the role of polymorphisms within some specific genes (eg, *COMT* and *OPRM1*) on cancer pain has been validated in several studies with adequate samples of patients, the majority of genetic polymorphisms in current genetic association studies need to be replicated to confirm these findings.

As described earlier, genetic variability is seemingly one of contributing factors that alter individual susceptibility to pain and response to opioid drugs in patients with cancer. In the era of precision medicine, biomarker-based diagnosis and treatment will be quickly replacing the traditional medicine, so-called “trial and error.”¹² Given that genetic biomarkers can help determine the efficacy and toxicity of analgesic drugs and predict the treatment response and symptom outcomes, cancer pain could be effectively managed with selected therapies that are personalized.^{12,51,66} If tests related to polymorphic genes with good sensitivity and specificity are clinically available for cancer pain, patients with cancer pain could benefit from improved quality of life and reduced health care utilization and costs.^{61,67} With a growing number of biomarkers developed for clinical use, health care providers will play a key role in identifying patients at high risk of cancer pain and evaluating the outcome of therapies or interventions, as well as educating patients on the interpretation of biomarker testing data.⁶⁸ Especially, nurses are in a unique position to apply this information to planning and using tailored pain management interventions and to help patients and families make a decision on selection of treatments over the cancer

trajectory.⁶⁹ Therefore, nurses should be prepared to have genomic and genetic competencies in assessment, education, and management of this specific patient population in clinical practice.⁶⁹

Although several candidate genes have been recognized with regard to cancer pain and analgesic responses, genetic association studies are still challenging because of the complex traits of genes and phenotypes. There are a number of environmental, psychological, and clinical factors that interact with genes involved in pain perception and analgesic effects.⁵⁴ Mostly, studies evaluating the association of genotypes with pain phenotype and opioid use likely provide confusing or limited information and do not consider effects of gene-gene or SNP-SNP interactions.^{54,70} In addition, large sample sizes to increase the power of studies and clear definition of clinical phenotype are important to genetic association studies.⁵⁴ Indeed, there is no consensus on cancer pain and how to address it (no specific assessment tools for cancer pain) in the studies included in this review. Nurse scientists should consider these issues when conducting genetic association studies.

Conclusion

Pain is the most common symptom in cancer patients, probably because of the cancer itself and cancer treatment. Genetic variability may have significant effects on differential pain perception and response to opioid treatment, but more studies are warranted to confirm the current findings in cancer pain. The information about genetic variants could offer optimal personalized treatment of cancer pain by determining drug efficacy and predicting the outcome of cancer pain. With growing evidence of genetic associations with symptoms, nursing practice and research should be integrated into personalized medicine in the treatment of cancer pain.

Funding Source:

This research was supported by the National Institutes of Health/National Institute of Nursing Research (F32NR018367 to G.S.Y. and P30NR016579 to S.G.D.).

References

1. Institute of Medicine (IOM). Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: National Academies Press; 2011 Available at: <https://www.ncbi.nlm.nih.gov/books/NBK91497/>. (Accessed January 4, 2019).
2. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst*. 2011;103:117–128. [PubMed: 21228314]
3. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage*. 2016;51:1070–1090 e1079. [PubMed: 27112310]
4. Bouhassira D, Luporsi E, Krakowski I. Prevalence and incidence of chronic pain with or without neuropathic characteristics in patients with cancer. *Pain*. 2017;158:1118–1125. [PubMed: 28267066]
5. Reyes-Gibby CC, Spitz M, Wu X, et al. Cytokine genes and pain severity in lung cancer: exploring the influence of TNF-alpha-308 G/A IL6-174G/C and IL8-251T/A. *Cancer Epidemiol Biomarkers Prev*. 2007;16:2745–2751. [PubMed: 18086782]
6. Portenoy RK. Treatment of cancer pain. *Lancet*. 2011;377:2236–2247. [PubMed: 21704873]

7. Mogil JS. Pain genetics: past, present and future. *Trends Genet.* 2012;28:258–266. [PubMed: 22464640]
8. Zorina-Lichtenwalter K, Meloto CB, Khoury S, Diatchenko L. Genetic predictors of human chronic pain conditions. *Neuroscience.* 2016;338:36–62. [PubMed: 27143481]
9. Dorsey SG, Resnick BM, Renn CL. Precision Health: Use of omics to optimize self-management of chronic pain in aging. *Res Gerontol Nurs.* 2018;11:7–13. [PubMed: 29370441]
10. Svetlik S, Hronova K, Bakhouch H, Matouskova O, Slanar O. Pharmacogenetics of chronic pain and its treatment. *Mediators Inflamm.* 2013;2013:864319. [PubMed: 23766564]
11. Reyes-Gibby CC, Shete S, Yennurajalingam S, et al. Genetic and nongenetic covariates of pain severity in patients with adenocarcinoma of the pancreas: assessing the influence of cytokine genes. *J Pain Symptom Manage.* 2009;38:894–902. [PubMed: 19692203]
12. Kalia M Personalized oncology: recent advances and future challenges. *Metabolism.* 2013;62(suppl 1):S11–14. [PubMed: 22999010]
13. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015;372:793–795. [PubMed: 25635347]
14. Bennett MI, Kaasa S, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. *Pain.* 2019;160:38–44. [PubMed: 30586069]
15. McCann B, Miaskowski C, Koettters T, et al. Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. *J Pain.* 2012;13:425–437. [PubMed: 22515947]
16. Rausch SM, Clark MM, Patten C, et al. Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. *Cancer.* 2010;116:4103–4113. [PubMed: 20564140]
17. Rausch SM, Gonzalez BD, Clark MM, et al. SNPs in PTGS2 and LTA predict pain and quality of life in long term lung cancer survivors. *Lung Cancer.* 2012;77:217–223. [PubMed: 22464751]
18. Reyes-Gibby CC, Spitz MR, Yennurajalingam S, et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. *Cancer Epidemiol Biomarkers Prev.* 2009;18:2636–2642. [PubMed: 19773451]
19. Reyes-Gibby CC, Wang J, Spitz M, Wu X, Yennurajalingam S, Shete S. Genetic variations in interleukin-8 and interleukin-10 are associated with pain, depressed mood, and fatigue in lung cancer patients. *J Pain Symptom Manage.* 2013;46:161–172. [PubMed: 23149083]
20. Yao P, Ding YY, Wang ZB, Ma JM, Hong T, Pan SN. Effect of gene polymorphism of COMT and OPRM1 on the preoperative pain sensitivity in patients with cancer. *Int J Clin Exp Med.* 2015;8:10036–10039. [PubMed: 26309696]
21. Cajanus K, Holmstrom EJ, Wessman M, Anttila V, Kaunisto MA, Kalso E. Effect of endocannabinoid degradation on pain: role of FAAH polymorphisms in experimental and postoperative pain in women treated for breast cancer. *Pain.* 2016;157:361–369. [PubMed: 26808012]
22. Oh SB, Tran PB, Gillard SE, Hurley RW, Hammond DL, Miller RJ. Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. *J Neurosci.* 2001;21:5027–5035. [PubMed: 11438578]
23. Shi Q, Cleeland CS, Klestad P, Miaskowski C, Pedersen NL. Biological pathways and genetic variables involved in pain. *Qual Life Res.* 2010;19:1407–1417. [PubMed: 20842532]
24. Brull DJ, Montgomery HE, Sanders J, et al. Interleukin-6 gene –174g>c and –572g>c promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. *Arterioscler Thromb Vasc Biol.* 2001;21:1458–1463. [PubMed: 11557672]
25. de Maat MP, Bladbjerg EM, Hjelmberg J, Bathum L, Jespersen J, Christensen K. Genetic influence on inflammation variables in the elderly. *Arterioscler Thromb Vasc Biol.* 2004;24:2168–2173. [PubMed: 15345506]
26. Burzotta F, Iacoviello L, Di Castelnuovo A, et al. Relation of the –174 G/C polymorphism of interleukin-6 to interleukin-6 plasma levels and to length of hospitalization after surgical coronary revascularization. *Am J Cardiol.* 2001;88:1125–1128. [PubMed: 11703956]

27. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A*. 1997;94:3195–3199. [PubMed: 9096369]
28. Roques BP, Fournie-Zaluski MC, Wurm M. Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain. *Nat Rev Drug Discov*. 2012;11:292–310. [PubMed: 22460123]
29. Andersen S, Skorpen F. Variation in the COMT gene: implications for pain perception and pain treatment. *Pharmacogenomics*. 2009;10:669–684. [PubMed: 19374521]
30. Klepstad P, Rakvag TT, Kaasa S, et al. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiol Scand*. 2004;48:1232–1239. [PubMed: 15504181]
31. Klepstad P, Fladvad T, Skorpen F, et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. *Pain*. 2011;152:1139–1145. [PubMed: 21398039]
32. Stephens K, Cooper BA, West C, et al. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. *J Pain*. 2014;15:169–180. [PubMed: 24411993]
33. Stephens KE, Levine JD, Aouizerat BE, et al. Associations between genetic and epigenetic variations in cytokine genes and mild persistent breast pain in women following breast cancer surgery. *Cytokine*. 2017;99:203–213. [PubMed: 28764974]
34. Fernández-de-las Peñas C, Fernandez-Lao C, Cantarero-Villanueva I, et al. Catechol-O-methyltransferase genotype (Val158met) modulates cancer-related fatigue and pain sensitivity in breast cancer survivors. *Breast Cancer Res Treat*. 2012;133:405–412. [PubMed: 21898113]
35. Kambur O, Kaunisto MA, Tikkanen E, Leal SM, Ripatti S, Kalso EA. Effect of catechol-o-methyltransferase-gene (COMT) variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. *Anesthesiology*. 2013;119:1422–1433. [PubMed: 24343288]
36. Bortsov AV, Devor M, Kaunisto MA, et al. CACNG2 polymorphisms associate with chronic pain following mastectomy. *Pain*. 2019;160:561–568. [PubMed: 30371558]
37. Langford DJ, Paul SM, West CM, et al. Variations in potassium channel genes are associated with distinct trajectories of persistent breast pain after breast cancer surgery. *Pain*. 2015;156:371–380. [PubMed: 25599232]
38. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol*. 2012;30:936–942. [PubMed: 22331951]
39. Laroche F, Coste J, Medkour T, et al. Classification of and risk factors for estrogen deprivation pain syndromes related to aromatase Inhibitor treatments in women with breast cancer: a prospective multicenter cohort study. *J Pain*. 2014;15:293–303. [PubMed: 24365325]
40. Mao JJ, Chung A, Benton A, et al. Online discussion of drug side effects and discontinuation among breast cancer survivors. *Pharmacoepidem Drug Saf*. 2013;22:256–262.
41. Garcia-Giralt N, Rodriguez-Sanz M, Prieto-Alhambra D, et al. Genetic determinants of aromatase inhibitor-related arthralgia: the B-ABLE cohort study. *Breast Cancer Res Treat*. 2013;140:385–395. [PubMed: 23868189]
42. Lintermans A, Van Asten K, Jongen L, et al. Genetic variant in the osteoprotegerin gene is associated with aromatase inhibitor-related musculoskeletal toxicity in breast cancer patients. *Eur J Cancer*. 2016;56:31–36. [PubMed: 26798969]
43. Young EE, Kelly DL, Shim I, Baumbauer KM, Starkweather A, Lyon DE. Variations in COMT and NTRK2 influence symptom burden in women undergoing breast cancer treatment. *Biol Res Nurs*. 2017;19:318–328. [PubMed: 28205449]
44. Furfari A, Wan BA, Ding K, et al. Genetic biomarkers associated with changes in quality of life and pain following palliative radiotherapy in patients with bone metastases. *Ann Palliat Med*. 2017;6(suppl 2):S248–S256. [PubMed: 29156910]
45. Liu J, Tang X, Shi F, et al. Genetic polymorphism contributes to (131)I radiotherapy-induced toxicities in patients with differentiated thyroid cancer. *Pharmacogenomics*. 2018;19:1335–1344. [PubMed: 30430914]

46. Sumitani M, Nishizawa D, Nagashima M, et al. Association between polymorphisms in the purinergic P2Y₁₂ receptor gene and severity of both cancer pain and postoperative pain. *Pain Med*. 2018;19:348–354. [PubMed: 28472364]
47. De Gregori M, Diatchenko L, Belfer I, Allegrì M. OPRM1 receptor as new biomarker to help the prediction of post mastectomy pain and recurrence in breast cancer. *Minerva Anestesiol*. 2015;81:894–900. [PubMed: 25300626]
48. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13:e58–68. [PubMed: 22300860]
49. Dy SM, Asch SM, Naeim A, Sanati H, Walling A, Lorenz KA. Evidence-based standards for cancer pain management. *J Clin Oncol*. 2008;26:3879–3885. [PubMed: 18688056]
50. Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. *J Clin Oncol*. 2014;32:1662–1670. [PubMed: 24799466]
51. Kapur BM, Lala PK, Shaw JL. Pharmacogenetics of chronic pain management. *Clin Biochem*. 2014;47:1169–1187. [PubMed: 24912048]
52. Mercadante S Prospects and challenges in opioid analgesia for pain management. *Curr Med Res Opin*. 2011;27:1741–1743. [PubMed: 21770715]
53. Al-Sayed AA, Al-Numay AM. Update and review on the basics of pain management. *Neurosciences (Riyadh)*. 2011;16:203–212. [PubMed: 21677608]
54. Droney J, Riley J, Ross JR. Evolving knowledge of opioid genetics in cancer pain. *Clin Oncol (R Coll Radiol)*. 2011;23:418–428. [PubMed: 21612899]
55. Yu Z, Wen L, Shen X, Zhang H. Effects of the OPRM1 A118G polymorphism (rs1799971) on opioid analgesia in cancer pain: a systematic review and meta-analysis. *Clin J Pain*. 2019;35:77–86. [PubMed: 30028366]
56. Gong XD, Wang JY, Liu F, et al. Gene polymorphisms of OPRM1 A118G and ABCB1 C3435T may influence opioid requirements in Chinese patients with cancer pain. *Asian Pac J Cancer Prev*. 2013;14:2937–2943. [PubMed: 23803057]
57. Cajanus K, Kaunisto MA, Tallgren M, Jokela R, Kalso E. How much oxycodone is needed for adequate analgesia after breast cancer surgery: effect of the OPRM1 118A>G polymorphism. *J Pain*. 2014;15:1248–1256. [PubMed: 25239082]
58. Hajj A, Halepian L, Osta NE, Chahine G, Kattan J, Rabbaa Khabbaz L. OPRM1 c.118A>G polymorphism and duration of morphine treatment associated with morphine doses and quality-of-life in palliative cancer pain settings. *Int J Mol Sci*. 2017;18(4).
59. Rakvåg TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain*. 2005;116:73–78. [PubMed: 15927391]
60. Matsuoka H, Makimura C, Koyama A, et al. Prospective replication study implicates the catechol-O-methyltransferase Val(158)Met polymorphism as a biomarker for the response to morphine in patients with cancer. *Biomed Rep*. 2017;7:380–384. [PubMed: 28928973]
61. Campa D, Gioia A, Tomei A, Poli P, Barale R. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. *Clin Pharmacol Ther*. 2008;83:559–566. [PubMed: 17898703]
62. Reyes-Gibby CC, El Osta B, Spitz MR, et al. The influence of tumor necrosis factor- α -308 G/A and IL-6 -174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. *Cancer Epidemiol Biomarkers Prev*. 2008;17:3262–3267. [PubMed: 18990769]
63. Lötsch J, Klepstad P, Doebering A, Dale O. A GTP cyclohydrolase 1 genetic variant delays cancer pain. *Pain*. 2010;148:103–106. [PubMed: 19959292]
64. Giacalone A, Polesel J, De Paoli A, et al. Assessing cancer-related fatigue: the psychometric properties of the Revised Piper Fatigue Scale in Italian cancer inpatients. *Support Care Cancer*. 2010;18:1191–1197. [PubMed: 19784676]
65. Gutteridge T, Kumaran M, Ghosh S, et al. Single-nucleotide polymorphisms in TAOK3 are associated with high opioid requirement for pain management in patients with advanced cancer admitted to a tertiary palliative care unit. *J Pain Symptom Manage*. 2018;56:560–566. [PubMed: 30031856]

66. Collins M Genetic risk factors for soft-tissue injuries 101: a practical summary to help clinicians understand the role of genetics and ‘personalised medicine’. *Br J Sports Med*. 2010;44:915–917. [PubMed: 19553227]
67. Bell GC, Donovan KA, McLeod HL. Clinical implications of opioid pharmacogenomics in patients with cancer. *Cancer Control*. 2015;22:426–432. [PubMed: 26678969]
68. Miaskowski C, Aouizerat BE. Biomarkers: symptoms, survivorship, and quality of life. *Semin Oncol Nurs*. 2012;28:129–138. [PubMed: 22542321]
69. Williams JK, Katapodi MC, Starkweather A, et al. Advanced nursing practice and research contributions to precision medicine. *Nurs Outlook*. 2016;64:117–123. [PubMed: 26712384]
70. Ross JR, Riley J, Taegetmeyer AB, et al. Genetic variation and response to morphine in cancer patients: catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. *Cancer*. 2008;112:1390–1403. [PubMed: 18257092]
71. Hattersley AT, McCarthy M. What makes a good genetic association study?. *Lancet*. 2005;366:1315–1323. [PubMed: 16214603]
72. National Library of Medicine (US). Genetics home reference. Available at: <https://ghr.nlm.nih.gov/primer/genomicresearch/snp>. Updated February 12, 2019. (Accessed February 13, 2019).
73. National Cancer Institute (NCI). NCI dictionary of genetics terms. Available at: <https://www.cancer.gov/publications/dictionaries/genetics-dictionary>. (Accessed February 13, 2019).
74. Sangkuhl K, Berlin DS, Altman RB, Klein TE. PharmGKB: Understanding the effects of individual genetic variants. *Drug Metab Rev*. 2008;40:539–551. [PubMed: 18949600]
75. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89–95.

Table 1

Genetic polymorphisms associated with cancer pain.

Gene	SNP rsID	Nucleotide Change	Pathway/Function	Associated Pain Phenotype	Type of Cancer	Study
IL-8		–251T>A	Inflammation	Pain severity	Lung cancer (white patients)	Reyes-Gibby et al, 2007 ⁵
IL-8		–251T>A	Inflammation	Pain	Lung cancer (NSCLC)	Reyes-Gibby et al, 2013 ¹⁹
IL-8		–251T>A	Inflammation	Pain	Pancreatic cancer (white patients)	Reyes-Gibby et al, 2009 ¹¹
IL-10	rs1800871		Inflammation	Pain	Lung cancer	Rausch et al, 2010 ¹⁶
NFKBIA	rs8904	C>T	Inflammation	Pain	Lung cancer	Reyes-Gibby, Spitz et al, 2009 ¹⁸
TNF-α	rs1800629	–308G>A	Inflammation	Pain severity	Lung cancer (non-Hispanic white)	Reyes-Gibby, Spitz, et al, 2009 ¹⁸
PTGS2	rs5275	+837T>C	Inflammation	Pain severity	Lung cancer (non-Hispanic white)	Reyes-Gibby et al, 2009 ¹⁸
PTGS2	rs5277	Minor “G”	Inflammation	Pain severity	Lung cancer (white)	Rausch et al, 2012 ¹⁷
LTA	rs1799964	Minor “G”	Inflammation	Pain severity	Lung cancer (white)	Rausch et al, 2012 ¹⁷
IL1R1	rs2110726	C>T	Inflammation	Preoperative breast pain	Breast cancer	McCann et al, 2012 ¹⁵
IL-13	rs1295686	G>A	Inflammation	Preoperative breast pain	Breast cancer	McCann et al, 2012 ¹⁵
FAAH	rs324420 rs1571138 rs3766246 rs4660928	C>A (Pro129Thr) G>A G>A C>A	Drug transport and metabolism	Preoperative experimental pain (cold pain sensitivity)	Breast cancer	Cajanus et al, 2016 ²¹
COMT	rs4680	G>A (Val158Met)	Neurotransmission	Preoperative pain sensitivity	Multiple types of cancer	Yao et al, 2015 ²⁰
OPRM1	rs1799971	118A>G (Asn40Asp)	Neurotransmission	Preoperative pain sensitivity	Multiple types of cancer	Yao et al, 2015 ²⁰

Abbreviations: Asn40Asp, a substitution of asparagine (Asn) for aspartate (Asp) at codon 40; COMT, catechol-O-methyltransferase; IL-8, interleukin 8; IL-10, interleukin 10; IL-13, interleukin 13; IL1R1, interleukin 1 receptor type 1; FAAH, fatty acid amide hydrolase; LTA, lymphotoxin alpha; NFKBIA, nuclear factor-kappa-B inhibitor alpha; NSCLC, non-small cell lung cancer; OPRM1, opioid receptor mu 1; Pro129Thr, a substitution of proline (Pro) for threonine (Thr) at codon 129; PTGS2, prostaglandin endoperoxide synthase 2; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor alpha; Val158Met: a substitution of valine (Val) for methionine (Met) at codon 158.

Table 2

Genetic polymorphisms associated with post-cancer treatment pain.

Gene	SNP rsID	Nucleotide Change	Pathway/Function	Associated Pain Phenotype	Type of Cancer	Study
IL1R2	rs11674595	T>C	Inflammation	Persistent postsurgical pain	Breast cancer	Stephens et al, 2014 ³²
IL-10 Haplotype A8	rs3024505	Minor "C"	Inflammation	Persistent postsurgical pain	Breast cancer	Stephens et al, 2014 ³²
	rs3024498	Minor "G"				
	rs3024496	Minor "C"				
	rs1878672	Minor "G"				
	rs1518111	Minor "A"				
	rs1518110	Minor "T"				
	rs3024491	Minor "T"				
IL-6	rs20069840	C>G	Inflammation	Persistent postsurgical pain	Breast cancer	Stephens et al, 2017 ³³
CXCL8	rs4073	T>A	Inflammation	Persistent postsurgical pain	Breast cancer	Stephens et al, 2017 ³³
TNF	rs1800610	C>A	Inflammation	Persistent postsurgical pain	Breast cancer	Stephens et al, 2017 ³³
COMT	rs4680	G>A (Val158Met)	Neurotransmission	Postmastectomy pain, pressure pain hypersensitivity	Breast cancer	Fernández-des-Ias-Peñas et al, 2012 ³⁴
COMT	rs165774 rs887200	G>A T>C	Neurotransmission	Experimental and acute postsurgical pain	Breast cancer	Kambur et al, 2013 ³⁵
COMT	rs4680 rs4818		Neurotransmission	Pain interference and severity	Breast cancer	Young et al, 2017 ⁴³
CACNG2 A-C-C haplotype	rs4820242 rs2284015 rs2284017	A>G C>G C>T	Neurotransmission (calcium channel)	Chronic postmastectomy pain	Breast cancer	Bortsov et al, 2018 ³⁶
KCNA1	rs4766311	C>T	Neurotransmission (potassium channel)	Persistent breast postsurgical pain	Breast cancer	Langford et al, 2015 ³⁷
KCND2	rs1072198	A>G	Neurotransmission (potassium channel)	Persistent breast postsurgical pain	Breast cancer	Langford et al, 2015 ³⁷
KCNJ3	rs12995382 rs17641121	T>C T>C	Neurotransmission (potassium channel)	Persistent breast postsurgical pain	Breast cancer	Langford et al, 2015 ³⁷
KCNJ6	rs858003	C>T	Neurotransmission (potassium channel)	Persistent breast postsurgical pain	Breast cancer	Langford et al, 2015 ³⁷
KCNK9	rs2542424 rs2545457	A>G T>C	Neurotransmission T>C (potassium channel)	Persistent breast postsurgical pain	Breast cancer	Langford et al, 2015 ³⁷

Gene	SNP rsID	Nucleotide Change	Pathway/Function	Associated Pain Phenotype	Type of Cancer	Study
CYP17A1	rs4919686 rs4919683 rs4919687 rs3781287 rs10786712 rs6163 rs743572		Drug transport and metabolism	Arthralgia	Patients with breast cancer treated with AIs	Garcia-Giralt et al, 2013 ⁴¹
CYP19A1	rs4775936		Drug transport and metabolism	Arthralgia (worsening pain)	Patients with breast cancer treated with AIs	Garcia-Giralt et al, 2013 ⁴¹
CYP27B1	rs4646536		Drug transport and metabolism	Arthralgia	Patients with breast cancer treated with AIs	Garcia-Giralt et al, 2013 ⁴¹
VDR	rs11568820		Drug transport and metabolism	Arthralgia	Patients with breast cancer treated with AIs	Garcia-Giralt et al, 2013 ⁴¹
OPG	rs2073618	G>C	Inflammation (cytokine receptor)	Musculoskeletal pain severity	Patients with breast cancer treated with AIs	Lintermans et al, 2016 ⁴²
P2RY12	rs3732765 rs9859538 rs17283010 rs11713504 rs10935840	C>T C>T C>T A>G A>G	Neurotransmission (purinergic signaling, activating microglia)	Pain severity, 24-hour postoperative pain (rs3732765)	Cancer pain patients	Sumitani et al, 2018 ⁴⁶
AQP7	rs76608797 rs33386144	C>A G>A	Other (water-selective membrane channel)	Pain	Bone metastases (patients undergoing palliative radiation therapy)	Furfari et al, 2017 ⁴⁴
PLAUR	rs4760		Other (regulation of cell surface protein and extracellular matrix)	Pain	Bone metastases (patients undergoing palliative radiation therapy)	Furfari et al, 2017 ⁴⁴
ELAC2	rs11545302	T>C	Other (tRNA processing and TGF- β signaling)	Pain	Bone metastases (patients undergoing palliative radiation therapy)	Furfari et al, 2017 ⁴⁴
TNF- α	rs1800629	-308G>A	Inflammation	Incidence of neck pain, throat pain	Differentiated thyroid cancer (patients receiving ¹³¹ I radiotherapy)	Liu et al, 2018 ⁴⁵
ATM	rs11212570		Other (DNA-damage response)	Throat pain	Differentiated thyroid cancer (patients receiving ¹³¹ I radiotherapy)	Liu et al, 2018 ⁴⁵
TNF- β	rs1800469 rs2241716		Inflammation	Throat pain	Differentiated thyroid cancer (patients receiving ¹³¹ I radiotherapy)	Liu et al, 2018 ⁴⁵
NF- κ B	rs230493		Inflammation	Throat pain	Differentiated thyroid cancer (patients receiving ¹³¹ I radiotherapy)	Liu et al, 2018 ⁴⁵

Abbreviations: AI, aromatase inhibitor; ATM, ataxia-telangiectasia mutated gene; AQP7, aquaporin 7; CACNG2, calcium channel voltage-dependent gamma subunit 2; COMT, catechol-O-methyltransferase; CXCL8, C-X-C motif chemokine ligand 8; CYP17A1, cytochrome P450 family 17 subfamily A member 1; CYP19A1, cytochrome P450 family 19 subfamily A member 1; CYP27B1, cytochrome P450 family 27 subfamily B member 1; ELAC2, ELA C Ribonuclease Z 2; IL-6, interleukin 6; IL-10, interleukin 10; IL1R2, interleukin 1 receptor type 2; KCNA1, potassium voltage-gated channel subfamily B member 1; KCND2, potassium voltage-gated channel subfamily D member 2; KCNJ3, potassium voltage-gated channel subfamily J member 3; KCNJ6, potassium voltage-gated channel subfamily K member 9; Leu193Pro, a substitution of leucine (Leu) for proline (Pro) at codon 193; NF- κ B, nuclear factor kappa B; OPG, osteoprotegerin; PLAUR, plasminogen activator urokinase receptor; P2RY12, purinergic receptor P2Y12; SNP, single nucleotide polymorphism; TGF- β , transforming growth factor beta; TNF, tumor necrosis factor; TNF- α , tumor necrosis factor alpha; TNF- β , tumor necrosis factor beta; tRNA, transfer ribonucleic acid; Val158Met, a substitution of valine (Val) for methionine (Met) at codon 158; VDR, vitamin D receptor.

Table 3

Genetic polymorphisms associated with response to opioids.

Gene	SNP rsID	Nucleotide Change	Pathway/Function	Associated Pain Phenotype	Type of Cancer	Study
OPRM1	rs1799971	118A>G (Asn40Asp)	Neurotransmission	Opioid requirement	Patients with cancer pain	Gong et al, 2013 ⁵⁶
OPRM1	rs1799971	118A>G (Asn40Asp)	Neurotransmission	Oxycodone requirement	Patients with postsurgical breast pain	Cajanus et al, 2014 ⁵⁷
OPRM1	rs1799971	118A>G (Asn40Asp)	Neurotransmission	Morphine consumption	Multiple types of cancer	Hajj et al, 2017 ⁵⁸
OPRM1	rs1799971	118A>G (Asn40Asp)	Neurotransmission	Morphine pain relief	Patients with cancer pain	Campa et al, 2008 ⁶¹
OPRM1	rs1799971	118A>G (Asn40Asp)	Neurotransmission	Morphine consumption	Patients receiving chronic morphine treatment	Klepstad et al, 2004 ⁴⁰
COMT	rs4680	G>A (Val158Met)	Neurotransmission	Morphine requirement	Patients with cancer pain	Rakvåg et al, 2005 ⁵⁹
COMT	rs4680	G>A (Val158Met)	Neurotransmission	Morphine requirement	Multiple types of cancer	Matsuoka et al, 2017 ⁶⁰
ABCB1	rs1045642	3435C>T	Drug transport and metabolism	Opioid requirement	Patients with cancer pain	Gong, et al, 2013 ⁵⁶
ABCB1/MDR1	rs1045642	3435C>T	Drug transport and metabolism	Morphine pain relief	Patients with cancer pain	Campa et al, 2008 ⁶¹
IL-6		-174G>C	Inflammation	Opioid consumption	Lung cancer	Reyes-Gibby et al, 2008 ⁶²
GCH1 haplotype	rs8007267 rs3783641 rs10483639	G>A A>T C>G	Neurotransmission	Opioid therapy initiation	Patients with cancer pain	Lötsch et al, 2010 ⁶³
TAOK3	rs1277441 rs795484	C>T A>G	Other (serine/threonine-protein kinase)	Opioid requirement	Multiple types of cancer	Gutteridge et al, 2018 ⁶⁵

Abbreviations: ABCB1, adenosine triphosphate (ATP)-binding cassette subfamily B, member 1; Asn40Asp: a substitution of asparagine (Asn) for aspartate (Asp) at codon 40; COMT, catechol-O-methyltransferase; IL-6, interleukin 6; GCH1, guanosine triphosphate cyclohydrolase 1; MDR1, multi-drug resistance gene; OPRM1, opioid receptor mu 1; SNP, single nucleotide polymorphism; TAOK3, TAO kinase 3; Val158Met: a substitution of valine (Val) for methionine (Met) at codon 158.

Table 4

Glossary terms.

Terminology	Description
Genetic association study	A type of study that aims to characterize and identify genomic variants that correlate with susceptibility to multifactorial diseases. ⁷¹
Single nucleotide polymorphism (SNP)	A type of human genetic variation that is abundant in the population. It involves the mutation of a single nucleotide in the DNA sequence. They are used as a resource for mapping many complex genetic traits. ⁷²
Genetic variability	The presence of genetic differences within a population.
Genetic variant	An alteration or variant in the typical DNA nucleotide sequence. Can be used to describe a benign or pathogenic alteration. ⁷³
Phenotype	The physical presentation of an individual who possesses a specific genotype. ⁷³
Genotype	The genetic composition of an individual. ⁷³
rsID	Stands for reference SNP ID. It is used by researchers and databases to refer to a specific SNP. ⁷⁴
Major allele	The dominant allele of the gene.
Minor allele	The recessive allele of a gene.
Heterozygous	A genotype that includes one major allele and one minor allele. ⁷³
Homozygous	A genotype that includes either two major alleles or two minor alleles. ⁷³
Biomarker	Biologic parameters that can be objectively measured and evaluated, which relate a specific therapeutic intervention to its effect on molecular and cellular pathways and its corresponding clinical presentation. ⁷⁵