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Genetic and pharmacogenomic influences on cancer pain management : A scoping review

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Short Report

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Abstract

Background: This article presents the findings from a scoping review which explored the genetic influence in cancer pain among cancer patients worldwide.

Objectives: To explore the genetic influence in cancer pain among cancer patients.

Setting: The review explored global literature on genetic influence in cancer pain among cancer patients.

Methods: The review was informed by the following questions: What specific genetic polymorphisms and epigenetic mechanisms have been investigated in relation to inter-individual variability in cancer pain perception and opioid response? What coping strategies are used in this context for cancer pain management? What is the range of reported clinical therapies and outcomes for cancer patients? What is the effect of genetic influence of cancer pain for care surgical nurses deliver to cancer patients?

Results: The review found that the 11 included studies employed the genetic influence on cancer pain with contrasting genetic factors, epigenetics, pharmacogenomics in cancer pain management and cancer pain coping strategies. Most of the studies reported outcomes associated with patients' reactions and positive changes in patients' attitudes/perceptions and improvement in knowledge/skills as a result in cancer pain management. In contrast, fewer studies reported changes in participant behaviors, changes in organizational practice and improvements to patients.

Conclusions: A number of educational, methodological and outcome implications are offered. Studying cancer pain management can enhance an education experience on cancer pain management, pain coping strategies, identification of genetic factors and epigenetic factors affecting for the cancer pain and genetic influence of narcotic drugs for cancer pain management.

Introduction

Pharmacogenomics has been a growing part of health professions education for over a decade (1). The report, which was conducted by the National Cancer Institute identified the gap in symptom by investigating multiple symptoms of cancer that might identify common biological mechanisms among cancer-related symptoms (2). Opioids are the major therapy for cancer patients affected by cancer pain and genetic variability account for the variation in individual responses to opioids, for both efficacy and toxicity (3). However, about 10%–20% of patients do not benefit from the received analgesic treatment or experience side effects (3).

Meta-analyses reporting the effects of opioid therapy have found that opioids are extensively used in patients with cancer pain, even though their efficacy among several patients experience ineffective analgesia and/or side effects (4). Advantages of pharmacogenetics are a new approach to drug prescription based on the "personalized medicine" concept by identifying specific genetic variants that influence pharmacokinetics and pharmacodynamics of drugs, better determining their effectiveness/safety profile (4).

It has been reported that patients with the combined OPRM1 118AG/GG and COMT 472GG genotype required 50% higher dose increase for sufficient analgesia however, consideration must be given to factors such as development of clear guidelines for educators regarding roles and responsibilities of cancer pain management, clear learner competencies regarding pharmacogenomics, access to genetical technology and sufficient funding for assessments (1). The interaction of multiple inflammation genes, along with nongenetic factors, underlies the occurrence of symptoms (2). In addition, according to the genome wide association study which was conducted in Italy, more than two thousand individually genotyped patients treated with opioids for cancer pain, that investigated the genetic bases of opioid-induced nausea-vomiting by identifying variants, and the importance of performing large pharmacogenomic studies to identify germline variants associated with opioid response, with the ultimate goal of tailoring cancer pain therapies (3).

Table 1: ***Overview of the framework for conducting a scoping study***

Review stage		Description
01.	Identifying the research question	Identifying the research question provides the roadmap for subsequent stages. Relevant aspects of the question must be clearly defined as they have ramifications for search strategies. Research questions are broad in nature as they seek to provide breadth of coverage.
02.	Identifying relevant studies	This stage involves identifying the relevant studies and developing a decision plan for where to search, which terms to use, which sources to be searched, time span and language. Comprehensiveness and breadth is important in the search. Sources include electronic databases, references list, hand-searching of key journals and organizations and conferences. Breadth is important; however, the practicalities of the search are as well. Time, budget and personal resources are potentially limiting factors and decisions need to be made upfront about how these will impact the search.
03.	Study selection	Study selection involves posthoc inclusion and exclusion criteria. These criteria are based on the specifics of the research question and on new familiarity with the subject matter through reading the studies.
04.	Charting the data	A data-charting form is developed and used to extract data from each study. A ‘narrative review’ or ‘descriptive analytical’ method is used to extract contextual or process-oriented information from each study.
05.	Collating, summarizing and reporting results	An analytical framework or thematic construction is used to provide an overview of the breadth of literature. A numerical analysis of the extent and nature of studies using tables and charts is presented. A thematic analysis is then presented. Clarity and consistency are required when reporting results.
06.	Consultation (optional)	This provides opportunities for consumer and stakeholder involvement to suggest additional references and provide insights beyond those in the literature.

However, it has been indicated that genetic influence in cancer pain may be viewed by some as isolating when compared with epigenetic influence of cancer pain due to limited resources for investigations genetic aspect (5). Further, it has been noted that technological difficulties can often be a key disrupting

factor (6), for example, it can result in a loss of gene association to understanding of the genetic susceptibility to cancer (7). When used to identify the association between the combined OPRM1(rs1799971)/COMT(rs4680) genotype which is related with a 50% higher relative increase in opioid dose required for sufficient analgesia after PCT consultation (1). Tumor microenvironment (TME) represents an element of increasing interest for the development of cancer immunotherapy as potential source of predictive factors for treatment with Immune Check point Inhibitors (ICI) or even as an additional therapeutic target by itself (8). Therefore, TME consists of a heterogeneous population of cancer cells, immune cells, vessels, stroma, signaling mediators and extracellular matrix proteins and the presence of a chronic inflammatory environment in cancer deviate immune cell differentiation, resulting in an imbalance of anti-tumor activity, thus favoring tumor evasion leading, resistance to ICI (8). Nevertheless, it has been found that this type of pharmacodynamics can help patients by adjusting the change in dose for the dose received at baseline, and the large variability between patients are reduced (1). As indicated above, patients with cancer-induced bone pain (CIBP) had more breakthrough pain, had greater difficulty in walking, used more adjuvant drugs, and had a slightly longer median overall survival than patients with non-CIBP. Patients with bone pain are carriers of a major symptom burden for a long time; thus, their management is clinically complicated and requires relevant attitudes and skills even though cancer pain influence negatively with genetic aspect of the patient (6).To fill this gap in knowledge, this review attempted to provide an overview of the empirical literature in order to generate an insight into the genetic influence in cancer pain.

Methods

Scoping reviews are being used increasingly by researchers to explore healthcare evidence (9). These reviews enable the clarification of complex areas of inquiry and refine subsequent research studies (9). The overall goal of a scoping review is to ‘examine the extent, range and nature of research activity, determine the value in undertaking a full systematic review, summarizing and disseminating research findings or identify gaps in the existing literature’ (9). We adopted a scoping review methodology to specifically examine the extent, range, and nature of evidence for the influence of genetics on cancer pain in primary healthcare teams. For this review, Arksey and O’Malley’s six-step framework for interpretive scoping literature reviews was used, with some small modifications (table 1) (9).

Identifying the relevant research question

Responding to the intention to explore the literature on genetic influence in cancer pain within primary healthcare, our research questions could focus on the following: map existing evidences of genetics which influence in cancer pain primary healthcare teams; generate an understanding of the influence of genetics for the cancer pain management and the depth and breadth of ‘the field’ and identify significant knowledge gaps and areas for improvement. With these initial ideas in mind, the following research questions were generated:

Box 1: Search terms
#1 Primary Care
#2 Care, Primary Care
#3 Health Care, Primary
#4 Care Primary
#5 General Practice
#6 #1 or #2 or #3 or #4 or #5
#7 Interprofessional or Inter-professional
#8 Interdisciplinary or Inter-disciplinary
#9 Multidisciplinary or Multi-disciplinary
#10 Team or Teamwork
#11 #7 or #8 or #9 or #10
#12 Genetics
#13 Cancer pain
#14 Evidence
#15 Influence
#16 Association
#17 #12 or #13 or #14 or #15 or #16

- What is the nature of evidence on genetic influence in cancer pain management for primary healthcare interprofessional teams?
- What pain-relieving approaches and coping methods are used for cancer patients in this context?
- What is the range of reported outcomes for cancer patients, their organizations and the care they are receiving regarding cancer pain?

Identifying relevant studies

Using the research questions as a guide, keywords were applied to a search strategy which was then preliminarily input into two electronic databases: Medline and CINAHL. This offered an indication of the relevance of the search terms, and the subsequent feasibility of their application was based on the numerical results generated from this preliminary search. This process enabled the following search strategy to be adopted (box 1).

Following consultation with university information scientists, in an attempt to gauge the efficacy of the strategy and identify further databases, these key terms were applied to six electronic sources. Including

studies from 2010 to 2025, the following databases were searched: Medline, CINAHL, Google Scholar, PubMed, Scopus, Web of Science

Box 2: *Journals searched*

Influence from genetic variability on opioid use for cancer pain: A European genetic association study of 2294 cancer pain patients: Experimental research – 2010

Genetic Variations in Interleukin-8 and Interleukin-10 Are Associated with Pain, Depressed Mood, and Fatigue in Lung Cancer Patients: Descriptive cross-sectional study - 2012

Impact of chronic pain on lung cancer incidence and mortality: Cohort study (Observational study) – 2014

Clinical and Genetic Factors Related to Cancer-Induced Bone Pain and Bone Pain Relief: Descriptive cross-sectional study - 2014

Advanced cancer pain: the search for genetic factors correlated with interindividual variability in opioid requirement: Observational study – 2017

Influence of genetic variants of opioid-related genes on opioid-induced adverse effects in patients with lung cancer: Observational study – 2018

Genetics and Opioids: Towards More Appropriate Prescription in Cancer Pain: Systematic review – 2020

Understanding the Psychological, Physiological, and Genetic Factors Affecting Precision Pain Medicine: Systematic review – 2021

Genetic Factors Associated with Pain Severity, Daily Opioid Dose Requirement, and Pain Response Among Advanced Cancer Patients Receiving Supportive Care: Prospective study – 2021

Genetic and Clinical Factors Associated with Opioid Response in Chinese Han Patients with Cancer Pain: Exploratory Cross-Sectional Study – 2022

Genomic Study in Opioid-Treated Cancer Patients Identifies Variants Associated with Nausea-Vomiting Descriptive cross-sectional study - 2025

An additional search of online and grey literature through Google and Google Scholar, and a further hand search of the 11 journals which have published the most papers found in the searches also took place (box 2).

From an initial yield of 110 potential sources (generated from electronic databases and additional searches), which through a rigorous screening process (see below), the review yielded 11 included studies (figure 1).

Study selection

In order to address the research question for this review, the following inclusion criteria were employed: Papers that describe evaluations of genetical influence for cancer pain involving interprofessional teams based in primary healthcare care in palliative centers and institutions where cancer patients are treated, all research evaluation designs (eg, action research, case study, ethnographic, experimental, quasi-

experimental studies), and any reported outcome from the cancer pain relieving strategies evaluation (see outcomes typology below).

As the searches and screening of potential sources progressed, it became apparent that there was very little literature reporting the genetic influence of cancer pain among cancer patients in primary healthcare centers and palliative centers. As a result, two key modifications were made to the inclusion criteria. First, the scope of review was widened to include pain coping strategies among cancer patients and cancer pain management. Second, the review was widened to include the genetic influence of cancer pain management.

Charting the data

Key information from the included studies was abstracted by combining a categorization of genetic influence of cancer pain (10) with an abstraction approach used in a previous systematic review (10). Using this approach, the following information was elicited from each of the studies included: Study aims/objectives, research design, sampling, data collection/analysis, location and duration of the intervention/activity in genetic influence of pain coping, impact of pain coping among cancer patients.

According to figure 1, searching results weremethods of pain coping by cancer patients, genetic influence of cancer pain in cancer patients, assessment/accreditation of cancer pain, and all reported outcomes of the genetic influence in cancer pain management

Collating, summarizing and reporting the results

Given the heterogeneous nature of the included studies, a thematic approach to the analysis was employed. This allowed the emergence of key issues (themes) from literature, enabling an insight into the methods of pain coping by cancer patients, genetic influence of cancer pain in cancer patients, and assessment/accreditation of cancer pain.

In addition, to capture the diversity of reported outcomes in the included papers, a Pain Coping Inventory (PCI) integrated into an extended Kirkpatrick/ Q4TE framework, which has four differing but non-hierarchical levels, was used (table 2).

Table 2: ***Key outcomes***

Outcome		Details
01.	Reaction	These outcomes cover patients' general views and perspectives on the cancer pain experience, its associated factors (genetic influence, family history), onset of cancer, type of pain (ex- radiating pain, burning pain), severity of pain.
02.	Acquisition of knowledge/skills	These outcomes relate to how the coping strategies affect cancer pain management, coping strategies for cancer pain management, ability of applying pain coping strategies for cancer patients during pain episodes and additional knowledge about cancer pain management (ex- pharmacological pain management techniques).
03.	Behavioral change	Outcomes at this level measure the coping level of cancer pain during pain episodes (relaxation/ breathing techniques), monitor symptoms during each pain episodes, distraction methods used to cope the pain (listen to music, watching Television), transfer of interprofessional skills and learning to workplace, such as support for change of behavior by documenting clinician reported items that patient apply consistently for pain coping or willingness of patients and nurses to apply new knowledge and skills about pain management strategies.
04.	Benefits to patients/clients	These outcomes cover any improvements in the ability of pain coping among cancer patients, health and well-being of patients/clients as a direct result of a programme, such as emotional status measures, cancer pain reporting incidence, duration or reducing rates of cancer pain, mortality, complication rates, readmission rates due to cancer pain, adherence rates, patient or family satisfaction, continuity of care, costs to carer or patient/client.

Methodological quality

All abstracts generated from the database searches (n=42) and additional searches (n=84) were reviewed independently by two of the authors to determine if they met the inclusion criteria (see above). The full text article was obtained (26 papers) if the abstract met these criteria. These articles were again screened independently by two authors as a second check to determine if they met the inclusion criteria.

Review limitations

There are three key limitations to this review. First, only English-language articles were considered for inclusion in the study. As such, we did not include potentially relevant materials written in other languages and published in non-English-speaking countries. Second, the review searched for materials published from 1994, so any papers published before this date were not included. Third, only a partial range of grey literature was searched. For example, we did not search primary healthcare conferences for possible materials. This restriction on grey literature was necessary to limit the volume of materials and maintain a focus on research studies.

Findings

Approaches of pain coping by cancer patients

Of the 11 included studies, 1 was undertaken in the USA, 5 were undertaken in Italy, 3 were undertaken in Norway, 2 were undertaken in the UK, 1 was undertaken in Germany, Sweden, Iceland, Switzerland, 1 in Japan, 2 in China, 1 in Netherland and Belgium. The professions represented included: medicine (2 studies), nursing (6 studies), pharmacy (8 studies), and genetics (10 studies).

Supplementary appendix 1 provides references for all included studies and Supplementary appendix 2 offers an overview of key contents of the papers reviewed, including aim of the methods of pain coping by cancer patients, genetic influence of cancer pain in cancer patients and assessment/accreditation of cancer pain genetic influence of cancer pain. As appendix 2 indicates, the included studies report on genetic influence on cancer pain in relation to the methods of coping by cancer patients. For example, in terms of severity of pain, location of pain, type of pain and pain coping strategies patients use.

Similarly, there was a wide range of different reviews and invitro studies, meta-analysis including 18 cancer sites, 99 genes, molecular mechanisms involved in the pharmacological effects, advancement of genetics and biomarkers testing, specific mutations leading. In addition, just over half of the studies did not mention the significant genetic influence on cancer pain management. This heterogeneity is also found in the mixture of differing pain coping approaches among cancer patients, types of cancers, medications given for pain management of cancer patients and genetic influence of medication used for cancer pain management. (supplementary appendix 2)

Genetic influence of cancer pain in cancer patients

Most studies employed meta and pooled analysis (eg, preintervention/postintervention, postintervention only) and typically gathered data in the form of (unvalidated) surveys. Five studies employed experimental design (randomized controlled trial, observational studies and prospective studies) though this study gathered validated survey data. There were also some uses of descriptive and exploratory cross-sectional studies (studies that gather quantitative data) that gathered interview and focus group data. Online supplementary appendix 3 presents an overview of information relating to key elements of the methodological approaches employed in each of the 11 studies. This appendix also indicates a wide variety in the sample sizes reported for the included studies ranging from 88 to over 467,169 participants. Most of the studies employed a convenience and random sampling techniques.

Assessment/accreditation of cancer pain

The review found that 8 of the 11 included studies provided reports of how the genetic factors of cancer patients influenced healthcare professionals to reduce cancer pain. Among these, one study stated that the epigenetic factors such as histone modification, DNA methylation, (p. 01) could improve impact on cancer pain management (11). Another study (5) that explored how genetic factors influence on pain severity. (12) study explored how pharmacogenomics affects for the cancer pain management. One

further study (13) found that it's important to have the knowledge regarding pain coping strategies for the cancer pain management (p. 363).

Reported outcomes

Table 3 provides an overview of studies which reported outcomes across the six-point outcomes typology (as presented in table 2).

Table 3: ***Overview of reported outcomes***

Outcome	No. of studies
Level 1: Reaction	05
Level 2: Acquisition of knowledge/skills	01
Level 3: Behavioural change	03
Level 4: Benefits to patients/clients	02
Total	11

As indicated in table 3, of the total number of outcomes (n=11) reported across the included studies, most (n=06) were associated with individual changes at levels 1, 2a and 2b. In contrast, fewer studies (n=05) reported broader changes at levels 3, 4a and 4b.

Discussion

Considering our research questions, the review indicated that the evidence in favor in identification on genetic influence on cancer pain is significant. Genetic influence in cancer pain management can both facilitate and improve interprofessional collaboration, improve quality of life of the patients and accessibility offer advantages which make preferable to more effective pain coping strategies for cancer patients. Genetic factors and epigenetics have the potential to facilitate cancer pain management and collaborative practice in primary healthcare and beyond. Taking place on a number of levels, these improvements can range from local team-based relations to global communication among cancer patients and multidisciplinary team members caring for cancer patients. Indeed, identification of genetic influence of cancer pain can offer a variety of useful opportunities to develop a range of collaborative competencies to improve pain coping strategies of patients (eg, genetic factors, epigenetics, pharmacogenetics in cancer pain management).

The review also identified that increasing intensity of healthcare practice often creates a distinctly time-sensitive environment, which can be alleviated by the identification of genetic influence on cancer pain management. Difficulties associated with cancer pain can be diminished as genetic factors and pharmacogenomics in cancer pain management is accessible and flexible for cancer patients. Genetic influence on cancer pain can therefore contribute to the development of competence of cancer pain

management of multidisciplinary team members as they can, for example, identification of genetic factors, epigenetics and pharmacogenomics related to cancer pain management help to reduce cancer pain of the patients and improve the quality of life of the cancer patients. As a result, identification of the genetic influence of cancer pain management can have a positive influence in the short and long term for cancer patients, benefiting healthcare team members to reduce the suffering of cancer patients due to pain as well as improving the care they deliver to patients. These findings resonate with research reporting the positive effects of genetic influence on cancer pain in the wider literature (14). Pain coping strategies among cancer patients can be regarded as invaluable to the coherent and efficient implementation of healthcare practice, it is important to identify and attempt to respond to any shortcomings or areas for improvement.

Conclusion/ Implications

Overall, the scoping review identified a number of key benefits related to the identification of genetic influence on cancer pain among cancer patients for cancer pain management. Its practicality was consistently reported to contribute to enhancing the quality of life of the cancer patients, identification of genetic and epigenetic factors for cancer pain, and identification of the genetic influence of narcotic drugs for cancer pain management. It was also reported that the pain coping strategies of cancer patients could be enhanced with the identification of genetic influence on cancer pain management, as cancer pain affects genetic factors, epigenetics, and pharmacogenomics related to cancer pain management (2,1,14).

Study outcomes

Collectively, the included studies indicated that the genetic influence on cancer pain among cancer patients generated a range of positive outcomes for participant reactions (level 1), helped to generate improvements to their pain coping strategies (level 2a), as well as improvements to their knowledge and skills for pain coping (level 2b). In addition, while the review indicated that the use of pain coping strategies resulted in gains to participants' individual behaviour (level 3), improvements in the way their care settings practiced (level 4a), and could generate benefits for patients (level 4b), fewer studies were reporting at these levels. While it is important to gather data for outcomes at levels 1, 2a, and 2b, future evaluations on cancer pain management should also focus on developing the evidence for its effects on levels 3, 4a and 4b (including genetic influence for the cancer pain management) to help build a more robust insight into the positive outcomes for the cancer patients. This focus on 'lower-level' outcomes is echoed in the wider interprofessional cancer pain management literature, which also found a propensity for studies to report on levels 1–2b so overlooking 'higher-level' outcomes (levels 3–4b) (3)(6).

Heterogeneity

While the included studies reported a promising number of outcomes associated with the genetic influence on cancer pain, the wide range of pain coping strategies does generate some limitations. Specifically, due to the heterogeneity of the genetic influence of cancer pain approaches reported in the

11 studies, it is easy to identify genes influencing cancer pain, impact on morphine to reduce cancer pain, influence on epigenetics and pharmacogenomics to reduce cancer pain (a problem which is compounded by the use of a mixture of differing study designs and methods). The problem of heterogeneity of interventions and evaluation approaches has been reported elsewhere in the literature regarding cancer coping strategies and genetic influence on cancer pain (5). Nevertheless, it is possible to note that of the included studies, those which employed a variety of approaches to reduce cancer pain as epigenetic regulation and pharmacogenetics influenced by narcotic drugs were well evaluated when compared with studies that only employed the genetic influence of cancer pain. In addition, blended approaches (using pain coping strategies for cancer pain management and genetic influence of narcotics for pain management) were also well evaluated. As noted above, such approaches have an impact on pain reduction of cancer patients by increasing quality of life of the cancer patients.

Self-report data

Another word of caution needs to be applied to the included studies. While the review indicated that these studies reported a range of positive outcomes related to the genetic influence of cancer pain, most of the 84 studies gathered data in the form of unvalidated surveys and focus groups. As a result, the bulk of outcomes are based on self-report data. This is a strong form of evidence as it is widely recognized genetic influence of narcotic drugs is related to cancer pain, epigenetics, and pharmacogenomics (3,4,11,1). As a result, such reports must be regarded as strong approaches to measuring change.

Abbreviations

Not applicable

Declarations

Clinical trial number

Not applicable

Ethics approval and Consent to participate

Ethical approval was not required for this scoping review as it involved analysis of previously published literature and did not include primary data collection from human participants.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declared no competing interest.

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Authors' contributions

UHTU were responsible for the study's conceptualization, project administration, and methodology, study's implementation and data collection processes. UHTU conducted the formal analysis, interpreted the findings, and authored the initial draft of the manuscript. UHTU revised the manuscript, ensured its organization, and contributed to refining its content. All authors reviewed the manuscript thoroughly and provided their approval for the final version, ensuring its accuracy and quality.

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Figures

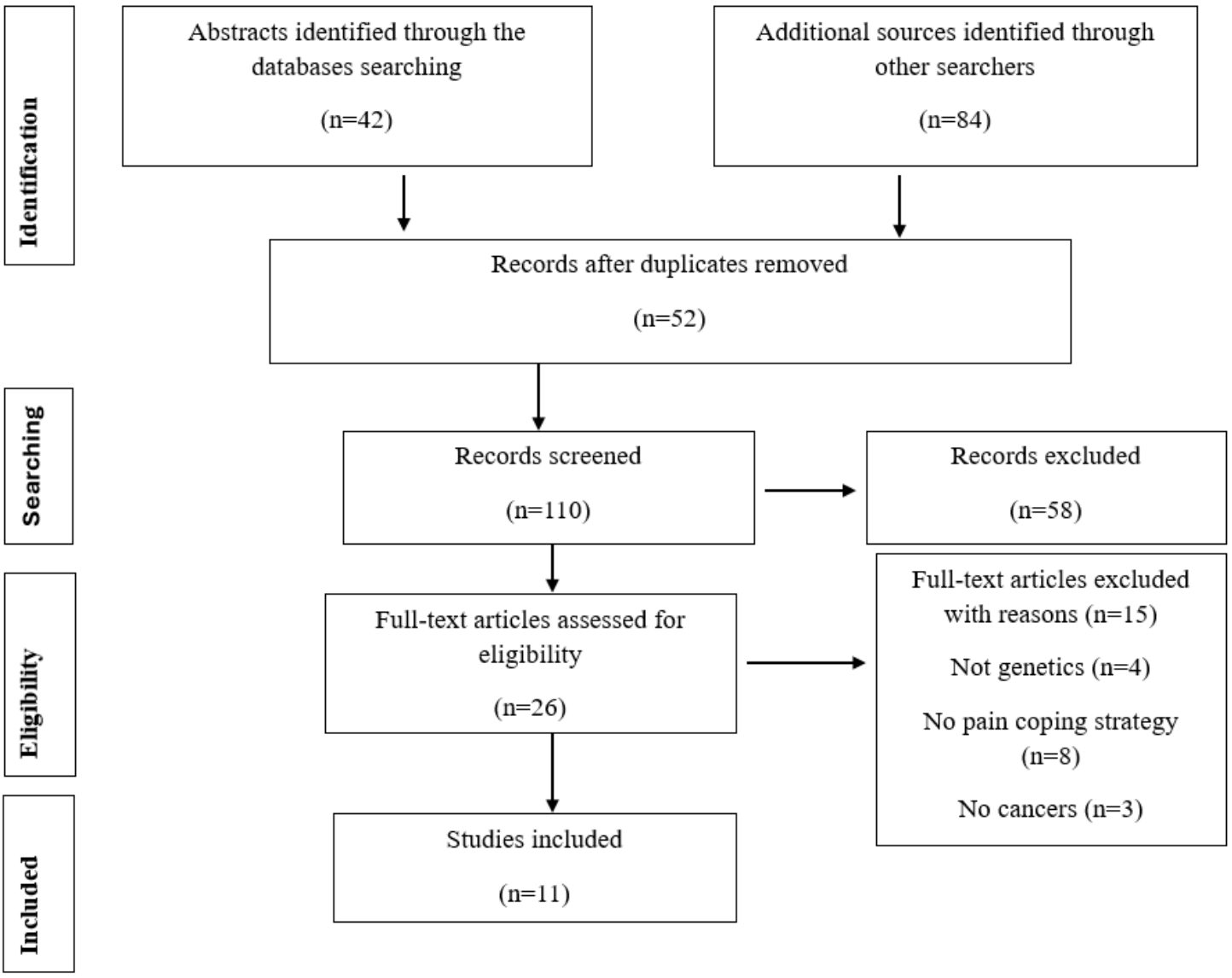


Figure 1

Searching and screaning results