Article Title: Complementary and Alternative Medicine Mention and Recommendations are Lacking in Colon Cancer Clinical Practice Guidelines: A Systematic Review

Jeremy Y. Ng [1]§ and Harmy Thakar [1]

[1] Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Michael G. DeGroote Centre for Learning and Discovery, Room 2112, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada

§Corresponding Author’s Email Address: ngjy2@mcmaster.ca

ORCiDs:
JYN: http://orcid.org/0000-0003-0031-5873

This is an author-produced postprint of an article accepted for publication on 7 June 2020 and published on 11 June 2020 in Advances in Integrative Medicine following peer review. The sharing of this postprint is compliant with the publisher policy as listed on Sherpa Romeo and can be found here: https://v2.sherpa.ac.uk/id/publication/24648.

This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

The published version of this article can be found at the following citation: Ng JY, Thakar H. Complementary and alternative medicine mention and recommendations are lacking in colon cancer clinical practice guidelines: A systematic review. Advances in Integrative Medicine. 2020 Jun 11. https://doi.org/10.1016/j.aimed.2020.06.002.
Abstract

**Background:** Cancer patients often utilize complementary and alternative medicine (CAM) in hopes that it will treat their disease and improve their physical and emotional well-being; past research has found that up to 80% of patients diagnosed with colorectal cancer use CAM. Caution must be taken, however, as some CAM therapies can be shown to be detrimental to patient health. This study identified the quantity and quality of recommendations associated with CAM in clinical practice guidelines (CPGs) for the treatment and/or management of colon cancer.

**Methods:** A systematic review was conducted to identify colon cancer CPGs. MEDLINE, EMBASE and CINAHL databases along with the National Centre for Complementary and Integrative Health (NCCIH) website were searched from 2008 to October 2018. The Guidelines International Network and the National Centre for Complementary and Integrative Health websites were also searched. It was originally planned that had eligible guidelines been found to contain CAM recommendations, they would have been assessed with the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument, however, none were found.

**Results:** From 160 unique search results, 8 CPGs were found to be eligible, however, no CPGs were found to make mention of CAM nor provide CAM recommendations. The CPGs found primarily discussed the effectiveness of conventional and adjuvant therapies, providing recommendations surrounding topics such as chemotherapy, radiotherapy, surgery, and the usage of oxaliplatin.

**Conclusions:** The quality of CAM versus overall recommendations could not be assessed in CPGs for the treatment and/or management of colon cancer, as no CAM recommendations were found in any of the eligible articles. Given that it is known that a high proportion of patients with colon cancer seek CAM, current colon cancer CPGs’ lack of CAM treatment or
management recommendations reflects a large gap in guidance for both clinicians and clinical researchers.

Abbreviations

AGREE II: Appraisal of Guidelines for Research & Evaluation II
CAM: Complementary and Alternative Medicine
CPGs: Clinical Practice Guidelines
NCCIH: National Center for Complementary and Integrative Health
PICO: Patients, Intervention, Comparison and Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

1. Background

Colon cancer refers to the initiation of a tumor in the tissues of the colon. The colon is a component of the large intestine that plays a role within the digestive system. Colon and rectal cancers are often grouped together as colorectal cancer because these organs are composed of the same tissues [1]. However, it is important to note that although colon and rectal cancer both affect the large intestine, they have unique treatment plans and prognoses. As such, to limit the ambiguity and increase specificity, this study focused exclusively on colon cancer only [2]. According to a study published in 2017 which assessed 37 countries via information from Cancer Incidence in Five Continents (CI5) volumes I–X and the WHO mortality database, the colon cancer incidence rate is expected to increase to more than 2.2 million new cases and 1.1 million deaths by 2030 [3]. With an increase in colon cancer patients, there has also been a steady increase in complementary and alternative medicine (CAM) usage among these individuals. Complementary medicine refers to treatments that are
used along with the standard medical treatment. In contrast, alternative medicine refers to treatments that are used instead of standard medical treatments [4].

It is known in the medical literature that cancer patients seek out CAM, despite advances in conventional cancer care for a number of reasons, including to lessen chemotherapy side effects, to support conventional treatment, or for disease symptom management [(5), (6), (7)]. Furthermore, cultural diversity and where a cancer patient lives, has been shown to play a role in the CAM therapy they may elect to use, for example with respect to the traditional medicines associated with their culture or country [8]. Specific to colon cancer, a recently published survey reported that 82.8% of colon cancer patients use CAM during their conventional therapy sessions [9].

Some of the most common CAM therapies used by colon cancer patients include herbal medicine and vitamins/minerals [10]. While comprising a wide range of unrelated therapies, for the purpose of this review we adopt the National Center for Complementary and Integrative Health (NCCIH)’s definition of CAM, which is “a group of diverse medical and health care interventions, practices, products or disciplines that are not generally considered part of conventional medicine” [11]. Vitamin/mineral treatment plans, along with spiritual therapy (i.e. meditation, hypnosis) and homeopathy have been found to be some examples of frequently used CAMs among cancer patients [12, 13]. Colon cancer patients often utilize CAM therapies for a number of reasons including: hope that they will improve their disease, belief that CAMs may minimize the toxicity within their body, and to feel more in control of the decision-making process of their illness [14]. Despite the high prevalence of CAM usage among colon cancer patients, many clinicians receive inadequate training on this subject area, and often lack the knowledge to effectively counsel patients [8,15].
Healthcare professionals rely on a wide variety of resources, including evidence-based clinical practice guidelines (CPGs) to guide appropriate clinical decision making. CPGs, in particular, are designed to help healthcare providers improve the quality of patient care by recommending therapies that have proven benefits while discouraging the use of ineffective or potentially harmful interventions [16]. To our knowledge, no prior research has investigated the quality or quantity of CAM recommendations in CPGs for the treatment and/or management of colon cancer. Thus, the purpose of this study was to conduct a systematic review to determine the mention of CAM in colon cancer CPGs and assess their quality using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument.

2. Methods

2.1. Approach

A systematic review was conducted to identify CPGs for the treatment and/or management of colon cancer using standard methods [17] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [18]. A protocol was registered with PROSPERO, registration number CRD42019132293. Had eligible CPGs with CAM recommendations been found, they would have been assessed with the widely used and validated AGREE II instrument [19]. The AGREE II instrument consists of 23 items grouped in six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence.
2.2. Eligibility criteria

Eligibility criteria for colon cancer CPGs were based on the Population, Intervention, Comparison and Outcomes framework. Eligible populations were adults aged 19 years and older with colon cancer. With respect to interventions, we only included CPGs that included treatment or management of colon cancer in order to determine what types of therapies were most commonly recommended. Eligible guidelines needed to base their recommendations, at least in part, using evidence found in the literature; entirely consensus-based guidelines were excluded. Comparisons would have involved assessing the quality of CAM versus overall recommendations in CPGs with CAM recommendations. When considering what therapies constituted CAM, we referred to a bibliometric and content analysis of CAM trials in the Cochrane Library by Wieland et al. which found that the CAM therapies most commonly evaluated in trials such as herbal supplements (non-vitamin, non-mineral dietary supplements or Chinese herbal medicine), acupuncture, and chiropractic or osteopathic manipulation [20]; while it should be clarified that we did not search for trials as part of this review, trial-based evidence is frequently used in the development of evidence-based CPGs, thus this resource was useful in restricting our definition of CAM for the purpose of this study. Outcomes were AGREE II scores which reflect guideline content and format. The following conditions were also applied to define eligible CPGs: developed by academic institutions, government agencies, disease-specific foundations, or professional associations or societies; published in 2008 or later, which provides a decade-long window into treatment/management CPGs for colon cancer providing at least five years since the publication of AGREE II (which provided developers with criteria for developing high-quality guidelines); English language; and either publicly available or could be ordered through our library system. Publications in the form of consensus statements, protocols, abstracts, conference proceedings, letters or editorials; based on primary studies that evaluated colon cancer management or treatment; or focused on colon
cancer curriculum, education, training, research, professional certification or performance were not eligible. It should be noted that only eligible CPGs that contained CAM therapy recommendations would have been assessed using the AGREE II instrument, in order to determine the difference in AGREE II scores between the overall guideline and specifically the CAM sections; only demographic information is reported for eligible guidelines that did not contain CAM therapy recommendations.

2.3. Searching and screening

MEDLINE, EMBASE and CINAHL were searched on October 11, 2018 from 2008 to October 9, 2018 inclusive. The search strategy (Supplementary File 1) included Medical Subject Headings and keywords that reflect terms commonly used in the literature to refer to colon cancer. We also searched the Guidelines International Network, a repository of guidelines [https://www.g-i-n.net/] using keyword searches restricted based on the eligibility criteria including “colon cancer” and “colonic neoplasms”. Next, we searched the National Center for Complementary and Integrative Health (NCCIH) website which contained a single list of CAM guidelines [https://www.nccih.nih.gov/health/providers/clinicalpractice]. HT and another research assistant screened titles and abstracts from all other sources. HT and the other research assistant screened full-text items to confirm eligibility. JYN reviewed the screened titles and abstracts and full-text items to standardize screening and helped to discuss and resolve selection differences between the two screeners.

2.4. Data extraction and analysis

The following data were extracted from each CPG and summarized: date of publication, country of first author; type of organization that published the CPG (academic institutions, government agencies, disease-specific foundations, or professional associations or societies);
and whether any CAMs were mentioned in this CPG. Had CAM been mentioned, it had also been planned to data extract the types of CAM mentioned, CAM recommendations made, CAM funding sources, and whether any CAM providers were part of the guideline panel, followed by assessment using the AGREE II instrument.

3. Results

3.1. Search results

(Fig. 1) Searches retrieved 219 items, 213 were unique, and 160 titles and abstracts were eliminated, leaving 53 full-text guidelines that were considered. Of those, 45 were not eligible, primarily because they were a position paper (n = 20), they could not be retrieved (n = 7), or did not meet other eligibility criteria (n = 18), leaving 8 CPGs eligible for review. Of these 8 CPGs, none were found to make mention of CAM or provide CAM recommendations.

3.2. Guideline characteristics

(Table 1) Eligible CPGs were published from 2010 to 2017 in Great Britain and Ireland (n = 2), Spain (n = 2), Switzerland (n = 2), Canada (n = 1), and the United States (n = 1) [[21], [22], [23], [24], [25], [26], [27], [28]]. The CPGs were funded and/or developed by professional associations or societies (n = 8). No CPGs made mention or recommendation of CAMs. Additional details regarding these CPGs are summarized in Table 1.

4. Discussion

The purpose of this research was to assess the quantity and evaluate the quality of CAM recommendations in CPGs for the treatment and/or management of colon cancer. Our intent was to identify credible, knowledge-based resources upon which patients and health care
professionals could base discussions and decisions about the use of CAM therapies for colon cancer. Unfortunately, none of the 8 eligible CPGs made mention nor recommendations of CAM. Had eligible CPGs contained CAM mention, they would have been assessed using the AGREE II instrument, however, we instead uncovered a knowledge gap in terms of resources available for clinicians encountering colon cancer patients inquiring about CAM.

Despite this, there have been other CPGs written on similar diseases, which have been assessed using the AGREE II instrument. In a guidance statement for colorectal cancer developed in 2012 by the American College of Physicians (ACP), each author independently reviewed 4 eligible CPGs via AGREE II. Although the total quantitative scores varied to an extent, the quantitative assessment of the guideline remained fairly consistent among the authors. All of the evaluated CPGs recommended screening adults who are at risk for colon cancer between 40 and 50 year of age. However, the choice of screening method varied between the CPGs. Overall, the CPGs scored the highest on the scope and purpose domain and lowest on the applicability domain [29]. Additionally, another study published in 2016 evaluated the quality of CAM CPGs, specifically CPGs on herbal medicines, acupuncture and spinal manipulation. Eligible CPGs assessed with AGREE II included CAM recommendations for a variety of diseases, including lung and breast cancer. Scaled domain percentages revealed that clarity of presentations was scored the highest among the CPGs at 85.3 % while applicability was once again scored the least at 20.7 %. For instance, it was found that out of 17 eligible CPGs, only one discussed facilitators and barriers to implementation of the recommendations while none addressed the resource implications of implementing the recommendations. Only three CPGs provided advice and/or tools to support the implantation of the recommendations while two provided monitoring and auditing criteria [30]. Additionally, it has been found that CAM recommendations across
CPGs of varying diseases/conditions vary both in quality and quantity [[32], [33], [34]]. The results from these aforementioned studies reveal some common poorly addressed components across CPGs, including those containing CAM-specific recommendations, highlighting what future guideline developers should focus on when developing CAM recommendations for colon cancer treatment and management.

Our finding that no CAM therapy recommendations exist in CPGs for the treatment and/or management of colon cancer reveals a major knowledge gap for both clinicians and clinical researchers. A search of CAM therapy trials for the treatment and/or management of colon cancer on the registry, ClinicalTrials.gov, yielded very few that have been registered. This is one reason that likely contributes to our finding even though we did not limit our inclusion criteria to only those CPGs informed by trial-based evidence. As a high proportion of patients with colon cancer seek CAM, it is imperative that CPGs begin to include CAM therapy recommendations. This finding is relevant to clinicians encountering colon cancer patients with CAM inquiries, those who will produce colon cancer CPGs in the future, and to developers of existing colon cancer CPGs. Apart from the AGREE II instrument, numerous other tools can be used to further support the development of colon cancer CPGs with CAM recommendations. Examples include GuideLine Implementability Appraisal (GLIA), Guideline Implementability Research and Application Network (GIRANet) and Implementability Framework and Guideline Implementability for Decision Excellence [31]. A consistency test can also be used to measure the similarity between the actual clinical practice and the guideline [32].
4.1. Strengths and weaknesses

This review was strengthened by a comprehensive and systematic search strategy across multiple academic databases. Weaknesses include the fact that we restricted our eligibility criteria to English-language CPGs based on the languages spoken by authors; understandably, CAM therapies exist across many regions of the world, including many countries where CPGs may be published in non-English languages.

Given that little research has investigated the existence of CAM recommendations in colon cancer CPGs, this review serves as a springboard for future investigations of such recommendations in similar cancer types. We specifically aimed to retrieve CPGs that specifically looked at colon cancer; we included CPGs that provided recommendations on more than one type of cancer (i.e. colon, rectal and anal), as long as they provided recommendations specific to colon cancer, as we assessed whether they included CAM therapies. However, this review would not have captured CAM therapy recommendations found in general cancer CPGs, which may be applicable to colon cancer patients, as a search for such CPGs would have been far more expansive and beyond the scope of this study. CAM-specific colon cancer CPGs, however, were accounted for, with none having been found on the NCCIH website, nor by a study conducted by the first author [30].

5. Conclusions

This study identified 8 eligible CPGs for colon cancer that were published between 2008 and October 2018. However, none of these CPGs mentioned CAM nor made CAM recommendations. Had any of the CPGs contained CAM recommendations, they would have been assessed using the AGREE II instrument. The fact that CAM therapies are not represented across CPGs for the treatment and/or management of colon cancer, despite a
large increase in published CAM research over the past several years, leaves clinicians underprepared to discuss the benefits or risks of these such therapies with patients compared to conventional therapies. This can lead to overuse or underuse of a CAM therapy rather than informed, safe and effective use. As an increased number of colon cancer patients turn to CAM therapies, it is of great importance that CPGs developed for the treatment or management of this condition implement CAM therapy recommendations. This would bridge the gap between patient demand and physician knowledge, encouraging well-informed and safe usage of CAM among patients. Future research should identify CAM therapies which are supported by enough evidence to serve as the basis for CPG development. Future research should also seek to compare the effectiveness of the most prevalently used CAM therapies for colon cancer in order to increase the efficacy of CAM recommendations made.

**Consent for publication**

All authors consent to this manuscript’s publication.

**Availability of data and materials**

All relevant data are included in this manuscript.

**Ethics approval and consent to participate**

This study involved a systematic review of peer-reviewed literature only; it did not require ethics approval or consent to participate.
Authors’ contributions
JYN: designed and conceptualized the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
HT: assisted with the collection and analysis of data, revised the manuscript critically and provided substantive edits, and gave final approval of the version to be published.

Funding
This study was unfunded.

Declaration of Competing Interest
The authors declare that they have no conflicts of interest.

Acknowledgements
We gratefully acknowledge Vanessa Kishimoto for assisting with screening and data extraction. JYN was awarded a Research Scholarship and an Entrance Scholarship from the Department of Health Research Methods, Evidence and Impact, Faculty of Health Sciences at McMaster University.

Supplementary data
Supplementary File 1: MEDLINE Search Strategy for Colon Cancer Clinical Practice Guidelines Executed October 10, 2018
References


Figures
Figure 1: PRISMA Diagram

MEDLINE (n=43)  
EMBASE (n=90)  
CINAHL (n=14)  
GIN* (n=17)  
NCCIH* (n=55)

Records after duplicates removed  
(n=213)

Titles/abstracts included based on eligibility  
(n=53)

Eligible CPGs  
(n=8)

CPGs that make mention of CAM*  
(n=0)

CPGs that make CAM recommendations and were assessed with AGREE II  
(n=0)

Titles/abstracts excluded  
(n=160)

Full text primary studies excluded  
(n=45)
- Newer guideline available (n=1)
- Position paper (n=20)
- Guideline summary (n=14)
- Published prior to 2008 on GIN (n=3)
- Irretrievable (n=7)
Table 1: Characteristics of Eligible Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Country</th>
<th>Developer</th>
<th>CAM Category</th>
<th>Guideline Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gollins 2017</td>
<td>Great Britain and Ireland</td>
<td>Association of Coloproctology of Great Britain &amp; Ireland</td>
<td>Not Applicable</td>
<td>Management of colon cancer</td>
</tr>
<tr>
<td>Moran 2017</td>
<td>Great Britain and Ireland</td>
<td>Association of Coloproctology of Great Britain &amp; Ireland</td>
<td>Not Applicable</td>
<td>Management of colon cancer</td>
</tr>
<tr>
<td>Meyers 2016</td>
<td>Canada</td>
<td>Cancer Care Ontario</td>
<td>Not Applicable</td>
<td>Adjuvant systemic chemotherapy for stages II III colon cancer</td>
</tr>
<tr>
<td>Labianca 2013</td>
<td>Switzerland</td>
<td>ESMO Guidelines Working Group</td>
<td>Not Applicable</td>
<td>Diagnosis, adjuvant treatment and follow-up for colon cancer patients</td>
</tr>
<tr>
<td>Maurel 2013</td>
<td>Spain</td>
<td>Spanish Society of Medical Oncology</td>
<td>Not Applicable</td>
<td>Adjuvant treatment of colorectal cancer</td>
</tr>
<tr>
<td>Zerey 2013</td>
<td>United States</td>
<td>Society of American Gastrointestinal and Endoscopic Surgeons</td>
<td>Not Applicable</td>
<td>Laparoscopic resection of colon cancer</td>
</tr>
<tr>
<td>Grávalos Castro 2010</td>
<td>Spain</td>
<td>Spanish Society of Medical Oncology</td>
<td>Not Applicable</td>
<td>Adjuvant treatment of colorectal cancer</td>
</tr>
<tr>
<td>Labianca 2010</td>
<td>Switzerland</td>
<td>ESMO Guidelines Working Group</td>
<td>Not Applicable</td>
<td>Diagnosis, adjuvant treatment and follow-up for colon cancer patients</td>
</tr>
</tbody>
</table>