TITLE

Interactions with the pharmaceutical industry and the practice, knowledge and beliefs of medical oncologists and clinical haematologists: a systematic review.

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ABSTRACT

Background: No previous review has assessed the extent and effect of industry interactions on medical oncologists and haematologists specifically.

Methods: A systematic review investigated interactions with the pharmaceutical industry and how these might affect the clinical practice, knowledge and beliefs of cancer physicians. MEDLINE, Embase, PsycINFO and Web of Science Core Collection databases were searched from inception to February, 2021.

Results: Twenty-nine cross-sectional and two cohort studies met the inclusion criteria. These were classified into three categories of investigation: 1. Extent of exposure to industry for cancer physicians as whole (n=11); 2. Financial ties among influential cancer physicians specifically (n=11), and; 3. Associations between industry exposure and prescribing (n=9).

Cancer physicians frequently receive payments from or maintain financial ties with industry, at a prevalence of up to 63% in the United States (US) and 70.6% in Japan. Among influential clinicians, 86% of US and 78% of Japanese oncology guidelines authors receive payments. Payments were associated with either a neutral or negative influence on the quality of prescribing practice. Limited evidence suggests oncologists believe education by industry could lead to unconscious bias.

Conclusions: There is substantial evidence of frequent relationships between cancer physicians and the pharmaceutical industry in a range of high income countries. More research is needed on clinical implications for patients and better management of these relationships.

Registration: PROSPERO identification number CRD42020143353

INTRODUCTION

Almost a fifth of the global medication market will be anticancer drugs by 2024, more than four times the nearest competing therapeutic area.(1) Sales representatives from the pharmaceutical industry routinely approach medical oncologists and haematologists, the prescribers of these medications, who are described together here as 'cancer physicians'. These interactions intend to affect prescribing practice and to maximize sales, which may have negative consequences for patient care.

Previous reviews have investigated the effect of these interactions on physicians in general. In 2000, Wazana found that physicians' attitudes towards interactions with industry representatives were mainly positive and that most studies showed an association between exposure to industry interactions and behaviours favouring promoted drugs.(2) Lotfi et al showed more variable attitudes towards these interactions in low-middle income countries, albeit based on a limited available body of evidence.(3) Regarding prescribing practice per se, Wazana's review showed consistent evidence for preferential and more costly prescribing following interaction with the pharmaceutical industry. Several subsequent systematic reviews supported these findings, demonstrating a general association between industry-provided information and payments and higher prescribing costs and frequency and lower prescribing quality.(4-7)

To our knowledge, following a literature and systematic review register search, no previous review has investigated the extent and effect of pharmaceutical industry interactions on the knowledge, beliefs or clinical practice of cancer physicians specifically. A review by Tibau et al showed in 2015 that reported rates of financial conflicts of interest for authors of clinical practice guidelines of anticancer drugs had increased over time, suggesting these interactions among practice-influencing clinicians are widespread and may lead to potential bias.(8) We performed a systematic review to investigate the extent of interactions with the pharmaceutical industry their effect on the clinical practice, knowledge and beliefs of cancer physicians.

METHODS

Protocol and registration

This review was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the identification number CRD42020143353, with a limited protocol available online.(9) The full protocol is available on request to the corresponding author and includes additional details about pre-specified methods. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria in designing and reporting this study (see Supplementary Appendix [S1]).(10)

Eligibility criteria

The target population was defined as practising medical oncologists and haematologists globally, including residents training in these specialties specifically. The investigated intervention was any interaction with the pharmaceutical industry. We aimed to identify any study that assessed either an association between interactions and behaviour or a prevalence of these interactions. This was kept purposefully broad to maximize the number of included studies.

The interactions could be either financial or non-financial, as long as they involved some form of direct contact with the pharmaceutical industry or its sales representatives. The relevant comparator was either a lower level or absence of these interactions. All interventional and observational studies with quantitative results were included.

Where studies investigated effects of interactions, the primary outcomes were any examples of affected clinical practice (such as prescribing behaviour), knowledge or beliefs following interaction with the pharmaceutical industry. These could be either objectively assessed or self-reported.

Knowledge referred to differences in level of cancer physicians' knowledge about specific aspects of patient care associated with different levels of exposure to pharmaceutical industry interactions. Beliefs referred to self-reported attitudes around interactions with the industry, including the perceived benefits or harms of these interactions.

We excluded editorials, perspectives, letters to the editor, case series, case reports and qualitative studies such as interviews, semi-structured interviews and focus group analyses. We also excluded both narrative and systematic reviews. Our included studies were limited to those in English, French or Italian. Studies investigating medical students, interns and pre-vocational resident medical officers were excluded. We had no geographic or time limit, nor any setting (i.e. clinical versus non-clinical) restriction.

Information sources and search strategy

To obtain relevant articles, we performed a systematic search using the MEDLINE, Embase and PsycINFO databases via the Ovid interface, in addition to the Web of Science Core Collection from their inception to September 2019, with the initial searches carried out on 9 October 2019. An updated search of all databases was performed on 19 February 2021. Additional citations were sought through Google Scholar and via a pre-planned forward citation search of included studies.

The search strategies were designed using a combination of keywords and medical subheading (MeSH) terms, tailored to each database. Each strategy was reviewed by two specialist medical librarians

following the Peer Review of Electronic Search Strategies (PRESS) guidelines(11), and are reported in detail in the Supplementary Appendix (S2).

The criteria used in the search were purposefully broad, so as to minimize the risk of omitting any relevant articles. For example, the initial searches included all articles with physicians as participants, rather than limiting these to cancer physicians specifically. When studies were identified that were not found in the initial search, we performed an additional search using an initially omitted MeSH term and keyword combination ('exp "Conflict of Interest"/ and (conflict of interest or conflicts of interest).tw and exp Oncologists/') in the Ovid-based databases to ensure no further citations were missed. These terms were additionally included in the updated search.

Study selection

A single reviewer (AP) screened all citations during the initial title and abstract screen to identify articles considered potentially suitable for inclusion. For the full-text screen of these, all papers were independently screened by five reviewers, working in pairs.

Prior to the full-text screen, we performed a pilot screen of five articles by all reviewers for calibration. When disagreement between two reviewers occurred during the formal full-text screen, a third reviewer independently adjudicated the final decision. We calculated Cohen's Kappa statistic to estimate inter-reviewer reliability for the decision to include a paper.

Data collection process and extracted items

We extracted data from the included studies using the standardized data extraction headings for systematic reviews of aetiology and risk provided by the Joanna Briggs Institute (JBI) Reviewer's Manual.(12) Data were initially extracted by a single reviewer (AP) and confirmed by a second (BM).

In line with the JBI recommendations, relevant data from each study included baseline details about the study, its methodology and characteristics, dependent variable (outcomes), the data analysis methods used and the study results.

Quality assessment

To assess the quality of individual studies, we used the critical appraisal tools provided by the JBI Reviewer's Manual. These assessments were performed independently by two reviewers (AP and BM) and investigated the studies as a whole rather than focusing on specific outcomes. Disagreements in the quality assessment were resolved by discussion, with no studies requiring third-reviewer adjudication, although this had been planned if necessary. Authors of any included studies were not involved in the selection, data extraction and quality assessment of these studies.(13-16) An external

reviewer (PD – see acknowledgements) was engaged for three studies to minimize bias in the assessments, as all other potential reviewer pairings involved either authors of or close professional relationships with the authors of these studies.(14-16)

Summary measures and synthesis

We undertook a descriptive analysis of the included studies, presenting their characteristics, settings and populations. Given the heterogeneous and observational nature of all the identified studies, we were unable to produce any summary statistics of effect. Instead, we categorized the studies by their focus of investigation and discussed the results using a qualitative synthesis approach.

When articles included cancer physicians as a subgroup, we reported results for these participants only. If relevant, we additionally reported on comparisons between cancer physicians and other physician groups.

Publication and sponsorship bias

We prospectively planned to look for both publication bias and sponsorship bias in the included studies as a whole. However, publication bias could not be assessed due to the lack of suitable studies for a meta-analysis required to perform inverted funnel plots of results against sample size. We collected data on funding sources and author conflicts of interest (if reported) for each included study.

RESULTS

Study selection

The search flow is displayed in Figure 1, including reasons for exclusion at the full-text review stage. Of the 5,150 unique articles identified through our searches, 31 reports met our inclusion criteria for the final qualitative analysis. The kappa statistic for the full-text screening was 0.730, considered substantial for inter-reviewer reliability.

Figure 1 here

Study characteristics

The characteristics of each study are described in Table 1. All identified studies were observational, with no assessments of planned interventions. All the studies were conducted retrospectively, and a majority (n=29) were cross-sectional studies with analysis carried out over a single time period. The remaining two were retrospective cohort studies.

Among the 31 study reports, we identified three broad categories of analysis: 1. Exposure assessments, or investigations of prevalence of exposure to the pharmaceutical industry for cancer physicians in general, predominantly through receipt of payments or attendance at events, as well as attitudes and beliefs around such exposure (n=11); 2. Financial ties among influential physicians specifically (trial and guideline authors), or investigations of potential bias in decision-making, predominantly through the conduct of clinical trials and clinical guidelines (n=11), and; 3. Prescribing outcome studies, or investigations of associations between industry exposure and prescribing (n=9).

Quality assessment of studies

The quality assessments for each study are presented in the Supplementary Appendix (S3 and S4), showing results across each critical appraisal domain using the JBI Reviewer's Manual using McGuinness's *robvis* program.(17) The most frequent areas of concern for the quality appraisal were the non-identification of and control for confounders. The studies that conducted surveys were also limited by low response rates and use of non-validated survey instruments. Concerns around the interpretation of specific studies are discussed in detail below.

Results of individual studies

The baseline characteristics of each study is described in Table 1. Summative descriptions of studies within each identified category are described below. Most studies (21 out of 31 [68%]) were based in the US, followed by Australia (5), Japan (3), Italy (1) and Canada (1). All studies were published from 2007 onwards, with a majority (n=27) published from 2016 onwards.

Table 1 here

Category 1: Investigations of exposure to the industry among cancer physicians in general

Table 2 here

As shown in Table 2, 11 studies directly analysed the frequency and types of exposure to the pharmaceutical industry, five with medical oncologist participants (18-22), one with haematologist participants (13) and five with both.(14, 15, 23-25) Three studies assessed industry payments made to all clinicians within the specialist subgroup.(20, 22, 23) These were widespread, with Marshall et al and Ozaki et al showing that 63% of US and 70.6% of Japanese medical oncologists received general payments in 2014 and 2016 respectively.(20, 22) In Australia, over a six month period between 2018

and 2019, 32% of medical oncologists and 31% of haematologists received non-research payments.(15) Among US clinicians active on Twitter, 72.4% received general payments in 2014.(24) Importantly, Inoue et al showed that between 2015 and 2017 80% of all payments made to US haematologists and oncologists were for non-research purposes.(25)

Two additional studies reported prevalence findings for payments, though the main findings of these papers related to associations with prescribing. Nonetheless, these showed that cancer physicians in the US receive payments at a higher prevalence than any other specialists.(26, 27) Similar findings were made for payments to Australian cancer physicians.(15) In addition, Behdarvand et al, Fabbri et al and Robertson et al all found evidence of oncology- and haematology-related industry-sponsored events in Australia occurring more frequently than or near the highest frequency of any subspecialty group.(13, 14, 21)

Attitudes around and prevalence of continuing medical education provided by the industry were assessed by DeCensi et al in Italy in 2017 and Lee et al in Australia in 2015.(18, 19) While limited by low response rates, both these studies showed widespread and poorly managed educational relationships with the industry. Most participants expressed a belief that they had adequate separation from industry, while concurrently most believed that unconscious bias in favour of a drug could arise from education sponsorship.

Category 2: Investigations of financial ties among influential cancer physicians

Table 3 here

As shown in Table 3, 11 studies analysed financial ties with the pharmaceutical industry among influential cancer physicians; nine with medical oncologist participants (16, 28-35), and two with haematologist participants (36, 37).

Six studies looked at the authors or editors of oncology or haematology trials or journals, to assess ties in these groups.(28, 30, 32, 34-36) These demonstrated financial relationships were reported by between 29 and 80% of clinicians, with one study showing that 79% of haematologists' financial ties were disclosed incompletely in published literature.(36) Medical oncologist authors were more likely than any other specialty to have financial ties, and incomplete disclosure of relationships in 32% of cases.(28, 34)

Five studies looked at financial ties among the authors of oncology clinical practice guidelines, leaders of representative societies and clinicians advocating for cancer drug funding, again consistently noting that these ties are widespread. (16, 29, 31, 33, 37) In 2014, 84% of National Comprehensive Cancer

Network guidelines authors for four common cancers received general payments, while 78.2% and 95%of Japanese oncology and haematology guidelines authors respectively received non-research payments between January 1 2016 and September 30 2017.(31, 33, 37) Lexchin found that 66.3% of submissions to the pan-Canadian Oncology Drug Review had some declared conflict, and 44.5% of all submissions had a financial conflict with the submission's drug manufacturer between 2016 and 2019.(29) Among oncologist leaders of the American Society of Clinical Oncology, approximately 80% received either general or research payments between 2017 and 2019.(16)

Category 3: Investigations of associations between industry exposure and prescribing

Table 4 here

As shown in Table 4, nine studies assessed associations between pharmaceutical industry exposure and prescribing. Four of these had medical oncologist participants (27, 38-40), and five had both haematologists and oncologists.(26, 41-44) All were based in the US, and eight used the Open Payments database as an exposure against Medicare prescribing data as a dependent variable.

Four studies assessed potential associations between industry payments and prescription rates of anti-cancer drugs. Two studies showed a small or negligible association between payments and prescription rates, although quality assessments raised concerns about both of these due to the identification and control of confounders as well as the validity of the exposure assessment.(27, 38) Prescribing outcomes were measured one year prior to exposure assessments in both studies, raising concerns about the validity of the outcome assessment; the results of these studies should therefore be interpreted with caution.

In contrast, Mitchell et al assessed the effect of payments prior to prescriptions in two studies, with an analytical focus on general payments.(41, 43) In both of these, for almost all cancer subtypes tested there were higher odds of prescribing specific manufacturers' drugs when oncologists received general payments by that company, if these were received consistently in the years prior. A single negative association for imatinib was potentially explained by contemporaneous introduction and promotion of nilotinib, made by the same manufacturer for the same indication.

Three studies assessed the broad cost of prescriptions following industry payments. Perlis et al found that haematologists and oncologists, combined as one group, had the highest relative non-research payments received of any specialty, with prescription costs increasing in a statistically significant linear fashion across all five quintiles of payments.(26) Hadland et al and Zezza et al both investigated the relationship between payments and the costs of opioid prescriptions, with Hadland specifically looking

at non-research payments.(39, 42) Using different methodological approaches, both studies showed that cancer physicians who received payments related to opioids had higher overall opioid prescription costs, particularly when payments were consistent over several years. Hollander et al looked at opioid-related gifts rather than payments per se, and again found higher levels of opioid prescribing among haematologists and oncologists when a greater value of gifts was received.(44)

Eisenberg et al performed the only study assessing the effect of introducing institutional marketing restriction policies on subsequent opioid prescribing.(40) This showed a small (1%) but significant difference in the percentage days of opioid prescribing between the period before and after the introduction of the policies, although it is unclear how these policies were enforced across different centres, meaning these results should be interpreted with caution.

Synthesis of results

We did not perform any quantitative synthesis (i.e. meta-analysis). This was partly due to the majority of studies being observational in nature, without measures of effect, and partly due to the heterogeneous design of the few studies that did measure effect. We were additionally therefore unable to quantitatively estimate differences in the magnitude or direction of outcomes based on study quality.

DISCUSSION

Key findings

This systematic review found strong evidence that cancer physicians frequently receive both general and research payments from the pharmaceutical industry or maintain financial conflicts of interest. When compared to other specialties, studies consistently show that cancer physicians receive payments at the highest or near highest rate of any specialty group. We found further evidence that 'key opinion leader' oncologists and haematologists (i.e. those whose positions within authoritative bodies are likely to influence broader practice) receive these payments at especially high amounts, suggesting a risk of bias internationally in the formation of clinical guidelines and high-impact journal publications.

Eight studies assessed prescribing practice of cancer physicians associated with payments from industry, and one looked at valuable gifts rather than payments. All of these found an association with prescribing, with either higher prescribing costs or preference for sponsors' drugs over others, particularly in the context of general payments. These findings are consistent with a recent review assessing the relationship between payments and physicians across all specialties.(7) All the assessed studies in this category in our review took place in the United States, which is explained by the greater

ease of accessing prescribing data in this study population for these drugs than other jurisdictions. No studies directly assessed patient outcomes, and only a single trial assessed the effect of limiting marketing on subsequent prescribing.(40)

Notably, all the studies of associations with prescribing practice related to drugs that are either orally or subcutaneously administered, due to limitations in the prescription data available for analysis. They did not assess prescription of intravenous anti-cancer medicines, including expensive novel agents such as immune checkpoint inhibitors.

Only two studies asked cancer physicians directly about their knowledge and beliefs around interactions with the industry, in Italy and Australia.(18, 19) The generalizability of both was limited by low response rates to the distributed surveys. Both suggested that oncologists believed that education by industry could lead to an unconscious bias in favour of the companies' products on the part of prescribers.

Strengths and limitations

This is the first systematic review directly assessing relationships between the pharmaceutical industry and cancer physicians specifically. It was strengthened by our clear methodological approach in line with the Joanna Briggs Institute Reviewer's Manual. Our search strategy underwent review by academic librarians at two institutions to enhance its validity, following PRESS guidelines, and our reporting followed PRISMA guidelines.

However, the review had two major limitations. First, our initial title and abstract screen was performed by a single reviewer, which may have led to the inadvertent omission of relevant texts. Second, the review was limited by its specificity. By focusing directly on cancer physicians, studies were excluded in which cancer physicians were assessed but not reported as a specified subgroup. This therefore limited the breadth of results that could be included in the analysis.

It is additionally possible that some studies may have been missed due to the specificity of our search strategy, given that several studies were identified through the in-citation review, though the risk of this was minimised through our additional post-hoc search described in the Methods. All studies identified also occurred in high-income countries, limiting the applicability of the results to low and middle income countries.

How results relate to other data

The findings of this study are consistent with previous systematic reviews assessing relationships between the industry and physicians in general.(2-6) However, this review has demonstrated that

relationships with the industry are more common and more lucrative for cancer physicians than other specialty groups. It has additionally identified that 'key opinion leader' cancer physicians are specific targets of influence for the industry.

Meaning of results

This review has shown consistent evidence that cancer physicians are targeted by the pharmaceutical industry, and often more intensively than other specialists, and some evidence that there is a high likelihood their prescribing is influenced as a result. The results also demonstrate that cancer physicians frequently either have little awareness of this, or little resolve to alter their behaviour. The mandatory disclosure of payments from industry in several jurisdictions internationally has exposed ethically dubious relationships. While there is some evidence to suggest disclosing payments may lead advisors to avoid these,(45) there are no real world data so far that suggest disclosures have led cancer physicians to reduce their acceptance of payments from the pharmaceutical industry.

There is therefore a need for policy to manage these relationships. At the very least, cancer physicians in influential positions, such as guideline authors and journal editors, should be discouraged or prohibited from accepting general payments from industry. At least one previous study suggested that US Food and Drug Administration Oncology Drug Advisory Committee recommendations are not associated with financial conflicts of interest, although its interpretation is limited by an unclear number of clinicians on the Committee.(46)

Implications and future research

This is an area of ongoing research and investigation. No studies assessed the effect of industry interactions in a controlled, randomized manner, and only a single study looked at behaviour change following alteration of institutional policies.(40) While not impossible, performing a randomized trial would be practically very difficult, as the research question is one of unconscious behaviour in the standard practice of independent practitioners. Notably, controlled trials have been used in other specialties to assess the role of educational interventions on subsequent behaviour, for example in psychiatry residents.(47)

A reasonable alternative would be to perform further trials of mandated decreased interaction with industry, such as the Eisenberg study, with a focus on lucrative anti-cancer drugs rather than opioids. This review also demonstrated a clear paucity of quantitative research exploring the knowledge and beliefs of cancer physicians. If issues with recruitment could be overcome, studies could be performed to understand why cancer physicians as a group interact with the industry to such an extent. This would be valuable to help formulate management policies globally.

Conclusions

The power of cancer physicians to prescribe anti-cancer medicines is more lucrative to the pharmaceutical industry than any other specialty group. It is therefore imperative to understand how the industry attempts to influence these physicians, so that later research can focus on strategies to avoid or, at minimum, manage these interactions to the benefit of patient care.

In this review, consistent evidence was found internationally that cancer physicians maintain financial conflicts of interest with the pharmaceutical industry, particularly when in positions that are likely to influence wider practice. Additional evidence was found that these interactions are likely to affect prescribing practice in a negative way. There is limited evidence that cancer physicians acknowledge and understand that interactions with industry may lead to bias, but no studies assessed or discovered any intent to change the current level of interactions that occur. More studies are needed to investigate how these interactions affect practice.

ADDITIONAL INFORMATION

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AUTHORS' CONTRIBUTIONS

All authors contributed to the protocol development, selection of studies, interpretation of data and final manuscript. AP undertook the literature searches and extracted data. AP, BM and AF performed the quality appraisals.

ETHICS APPROVAL

No ethics approval was necessary as all data analysed exist in the public domain.

DATA AVAILABILITY

No additional data available.

COMPETING INTERESTS

In 2020, Barbara Mintzes acted as an expert witness for Health Canada in a legal case related to marketing of an unregistered product in Canada. There are no other conflicts to declare.

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591 FIGURE AND TABLE LEGENDS

Figure 1: PRISMA flow diagram

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Table 1: Characteristics of included studies

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Table 2: Prevalence of industry exposure among cancer physicians in general: key results.

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Table 3: Financial ties among influential cancer physicians (authors of clinical trials and guidelines): key results.

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Table 4: Associations between industry exposure and prescribing: key results.

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