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Medication overuse in oncology: current trends and future implications for patients and society

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Summary:

The high cost of cancer care worldwide is largely attributable to rising drugs prices. Despite their high costs and potential toxicities, anticancer treatments may be subject to overuse, defined as the provision of medical services that are more likely to harm than to benefit a patient. We found 30 studies documenting medication overuse in cancer, which included 16 examples of supportive medication overuse and 17 examples of anti-neoplastic medication overuse in oncology. Evaluated drugs were limited to relatively few specific agents, and no studies investigated overuse of the most toxic or expensive medications currently used in cancer treatment. While financial, psychological, or physical harms of medication overuse in cancer could be substantial, there is little literature addressing these harms so their magnitude is unclear. Further research is needed to better quantify rates of medication use, understand its implications, and help protect patients and the healthcare system from future overuse.

Introduction

The cost of cancer care is high and rising worldwide,[1] with cancer spending increasing by 75% in the UK between 2003 and 2010[2] and expected to rise 39% in the US between 2010 and 2020.[3] These cost increases are largely attributable to drugs. Drug prices increased 10% annually between 1995 and 2013 in the US and the average cost of systemic therapy doubled

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in the UK between 1995–1999 and 2005–2009;[4] globally anticancer drug costs are projected to reach $150 billion by 2020.[5] While drug costs vary across countries,[6–8] the unaffordability of cancer drugs is a global problem with particularly high impact in low- and middle-income countries such as China, India, and South Africa.[9,10] Concerns about the high cost of cancer care have led to an emphasis on value from professional societies such as the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO), which has developed the "magnitude of clinical benefit scale" to optimize appropriate use of limited resources to deliver affordable cancer care.[11]

Despite their high costs and potential toxicities, anticancer treatments may be subject to overuse. Overuse is defined as the provision of medical services that are more likely to harm than to benefit a patient.[12] Along with underuse and misuse, overuse is a fundamental quality problem in medicine that is recognized around the world[13] and has both clinical and financial implications. While rates of overuse vary across populations and by specific services, the Institute of Medicine has estimated that nearly 30% of US medical expenses are due to unnecessary or inefficient services, contributing to thousands of unexpected deaths.[14] Despite attention to the problem of overuse in recent years,[13] evidence of overuse in patients with cancer remains limited, with most studies focusing on diagnostic tests rather than treatments.[15,16] Reducing overuse is an attractive strategy for controlling costs while improving the overall quality of cancer care and optimizing patient outcomes.

In this paper, we review the literature on rates of overuse of medications in oncology, outline the potential associated clinical and financial harms, and discuss important areas for future research. Although our search design was agnostic to a country's socioeconomic status, we found only three evaluations of medication overuse in low and middle income countries (LMICs). Therefore, this review focuses primarily on medication overuse in high income countries and our findings are most applicable to this setting.

Measurement of Medication Overuse

Overuse in general and of medications in particular can be measured in several ways as shown in Table 1. The most reliable methodology for measuring overuse is with d*irect* measurement, in which practice is compared to a clear utilization standard, generally based on a guideline or appropriateness criteria. Any medication use outside of recommended practice would be considered overuse. This approach has inherent challenges because it requires clear agreed-upon guidelines for specific clinical situations.[13] For this reason, the number of medications for which there is direct measurement of overuse is limited, capturing only a small proportion of overall overuse.

Indirect measurement has commonly been used to capture overuse in situations in which there is no standard for determining appropriateness.[13] This is typically performed by studying variations in medication utilization across providers that are not explained by patient or disease characteristics. Although these variations may often be attributable to discretionary care,[17] unexpectedly high rates of use of a particular medication are likely to reflect overuse. In addition, an intervention effect can suggest overuse: reduction in medication use after implementation of a pathway or price change with no negative clinical

consequences implies overuse prior to the intervention. Of note our definition of an intervention effect did not include reduced medication use after a new safety concern. Such reductions likely reflect determinations of appropriateness based on current information about benefits and harms rather than inappropriate earlier use.

Search Strategy and Selection Criteria

For this review, we combined evidence from a recent systematic review of direct evidence of overuse of health services in oncology[15] with a search for additional evidence of medication overuse in oncology including indirect evidence and an update of the prior review. We focused on examples of overuse related to medication prescribing and/or administration by healthcare providers. The prior systematic review, which included articles published between December 1, 2011 and March 10, 2017, identified 8 examples of direct overuse of medications in cancer patients. Our search of the PubMed and EMBASE databases used keywords and subject headings related to medical/medication/drug overuse and misuse, as well as terms related to overtreatment and unnecessary treatment/procedures, adherence/non-adherence to practice guidelines, and variation in practice/prescribing patterns. The search sets were combined with keywords and controlled terms for cancer/oncology, and chemotherapy and the chemotherapy-associated therapies of interest. We reviewed bibliographies and cited references of all relevant identified papers using Web of Science to find additional studies. Our search was limited to articles published in English. We ultimately identified an additional 22 papers for a total of 30.

Evidence of Overuse: “What We Know”

The 30 studies we found identified 16 examples of overuse of supportive medications (Table 2) and 17 examples of overuse of anti-neoplastic medications (Table 3) in oncology. To our knowledge, none of the studies we found were funded by the pharmaceutical industry.

1. Overuse of supportive medications in oncology (Table 2)

Supportive medications improve the ability of patients to tolerate cancer treatment and are important components of cancer care. However, they may be used inappropriately. As part of the American Board of Internal Medicine (ABIM) Foundation’s Choosing Wisely Campaign, ASCO identified services that may be overused and that doctors and patients should question. Among 10 such services identified by ASCO, two relate to the use of supportive medications: anti-emetic medications and WBC growth factor support agents during chemotherapy.[18] We found studies documenting overuse of both of these types of medications.

Anti-emetics—Anti-emetics are important to help patients tolerate chemotherapy and maintain quality of life.[19] However, with the cost of a cycle of newer serotonin receptor antagonists reaching as high as $2000,[20] their financial impact necessitates thoughtful and evidence-based use. As a result, ASCO identified proper anti-emetic use as one of the five key opportunities to improve care and reduce costs in cancer.[18] To foster appropriate use, large oncology organizations worldwide[21–24] have developed guidelines stating when to use dexamethasone, serotonin receptor antagonists, and neurokinin 1 receptor antagonists to

prevent nausea and vomiting based on the emetogenic potential of a particular chemotherapy regimen, emphasizing use of less expensive and less effective agents in patients at lower risk for nausea and vomiting. For example, both ASCO and the Japanese Society of Clinical Oncology recommend dexamethasone alone as the preferred initial treatment to prevent nausea and vomiting for chemotherapies with low-emetogenic potential.[21,22]

We found six studies[25–30] that evaluated non-recommended use of more expensive anti-emetic drugs for primary prophylaxis in patients receiving low-emetogenic chemotherapy. These studies, performed in the US, Switzerland, Japan, China, Brazil, and India all measured overuse directly at the patient level. Estimated rates of overuse ranged from 24–70% across studies (Table 2). Notably, anti-emetics represent the only class of drug whose overuse in oncology has been studied in low and middle income countries (LMICs). One of these studies (Patil et al)[30] evaluated a single-center quality improvement intervention aimed at reducing overuse and found lower rates of anti-emetic overuse after the intervention.

Growth factor support agents—White blood cell growth factor support provided by granulocyte colony stimulating factors (GCSF) can minimize the risk of fever and neutropenia (FN) and reduce infection-related mortality in high-risk patients.[31,32] However, these medications have important side effects, including musculoskeletal pain in nearly 20% of patients,[20] and are expensive,[33] with costs of approximately $2000 per cycle.[20] The US Office of the Inspector General has estimated that the Centers for Medicare & Medicaid Services (CMS) paid approximately $1·7 billion for over one million claims for prophylactic GCSF injections between 2004 and 2007.[34] Clinical practice guidelines from both ASCO[35] and ESMO[36] recommend GCSF as primary prophylaxis only when the risk of FN from chemotherapy is 20% or higher.

Erythropoietin stimulating agents (ESAs) represent growth factor support to increase hemoglobin levels and reduce transfusion requirements in patients with anemia due to chemotherapy. ESAs are associated with potential harms including venous thromboembolism, stroke, tumor progression, and mortality.[37,38] ASCO[39] and ESMO[40] have both created evidence-based practice guidelines for the use of ESAs, although these guidelines do not provide concrete indications for ESA use.

We found 10 studies[20,41–49] that examined overuse of either GCSF or ESA. All were US-based and involved patients with solid tumor malignancies. Most studies of GCSF utilized direct evidence since clear guidelines exist, and estimates of overuse ranged from less than 10% to over 90% in patients receiving treatment regimens with less than a 20% risk of FN (Table 2). In contrast, four of the five studies investigating ESA overuse relied on indirect evidence. These studies found that ESA use varied widely geographically and based on spending patterns of practice groups, suggesting ESA overuse among high users. The single study that utilized direct evidence compared patient-level use to FDA-approved indications and found off-label ESA use in 13·6% of patients.[45] We did not include studies evaluating the impact of the 2007 FDA boxed warning on ESA use since reduced prescribing was likely due to improved knowledge of potential drug harms and not to prior overuse.

2. Overuse of anti-neoplastic medications in oncology (Table 3)

Systemic anti-neoplastic medications are the primary treatment for non-localized solid tumor cancers and all liquid tumor malignancies. The potential benefits of these treatments must be balanced against their potential harms which can be permanent or life-threatening. Given their toxicities, avoiding overuse of antineoplastic agents is crucial for protecting patient safety.

We found studies evaluating overuse of anti-neoplastic medications including cytotoxic chemotherapy, biologics, androgen deprivation therapy (ADT), and radioactive iodine (RAI). Most studies of anti-neoplastic medications were performed in the US; one study was in Canada.

Chemotherapy is broadly defined as any medication that targets rapidly dividing cancer cells[50] and is generally associated with a wide spectrum of toxicities resulting from detrimental effects on normal dividing cells. We identified seven studies[49,51–56] with eight evaluations of chemotherapy overuse. Studies focused primarily on colon and lung cancers and all were performed in the US or Canada.

Adjuvant chemotherapy is never recommended for stage I colon cancer.[57] One study directly evaluated overuse of adjuvant chemotherapy in patients with stage I colon cancer and found that rates varied geographically between 3·1% and 6·3% (Table 3).

Three studies evaluated overuse of chemotherapy indirectly based on an intervention effect (described in Table 1). Implementation of pathways reduced spending on chemotherapy by up to approximately $40,000 in colorectal cancer[52] and more than $12,000 in lung cancer.[53] In contrast, changes in Medicare reimbursement led to a shift towards using more profitable drugs such as docetaxel in lung cancer, suggesting overuse of these agents.[55]

Avoiding overuse of targeted therapies (which in this case are biologic medications) is among ASCO's Choosing Wisely recommendations.[18] The monoclonal antibody trastuzumab, which targets the human epidermal growth factor receptor 2 (HER2), is a targeted therapy that is recommended only in the approximately 15% of breast cancers that overexpress HER2.[58] It has important clinical harms including an increased risk of heart failure.[59] Two studies[60,61] evaluated the overuse of trastuzumab in women without known HER2 overexpression and found similar rates of overuse: 3·9% and 4·7% (Table 3).

Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF) receptor, is approved for several solid tumor malignancies including metastatic colorectal, ovarian, and lung cancers. The cost of a two week cycle of bevacizumab for colon cancer varies by country, ranging (in US dollars) from approximately $1,292 in Australia to $1,645 in Israel to $2,649 in the US, with potential life-threatening side effects including venous thromboembolic events and bowel perforation.[62] The lone study of bevacizumab overuse found that practices in the highest quartile of spending on cancer care are 2·2 times as likely to use bevacizumab as practices in the lowest spending quartile.[49]

Androgen deprivation therapies (ADT), including gonadotropin-releasing hormone (GnRH) agonists, have toxicities including osteoporosis, depression, and anemia. ADT is not

recommended as monotherapy for localized prostate cancer and is instead reserved for men with metastatic disease or as an adjuvant to radiation in some patients with higher-risk local disease.[63] In 2003, the Medicare Modernization Act (MMA) standardized Medicare reimbursement with an overall 50% reduction in ADT reimbursement rates.[64] Of the four studies[65–68] that evaluated ADT overuse, two analyses leveraged this policy change to investigate likely overuse, and found approximately 30% reductions in ADT use after 2003,[64,67] suggesting overuse prior to 2003, likely attributable to a financial incentive.

Radioactive iodine (RAI) is used to treat residual or presumed micrometastatic disease in patients with differentiated thyroid cancer disease. Because no benefit has been shown for stage I resected differentiated thyroid tumors,[69] RAI is not recommended for papillary cancers 1 cm or less, or for the non-differentiated medullary or anaplastic thyroid cancers. One large study evaluated RAI overuse in over 60,000 patients and found that 23·3% of patients received RAI inappropriately, at an estimated cost of between $5,429 and $9,105 per patient in 2014 US dollars.[70]

Implications of Medication Overuse

Medication overuse has important financial and clinical harms (Table 4). The financial harms include immediate and downstream costs that affect both individual patients and the healthcare system. Most simply, there is financial harm from the cost of the medication itself, which can be substantial. In this review, we found evidence of overuse of eight different medications. The cost of a cycle of treatment with each of these medications in select countries in Europe and North America is shown in **Table 5**. The high costs of some of these medications have important implications for cancer patients, many of whom suffer financially as a result of cancer treatment and are more likely than the general population to declare personal bankruptcy,[71] which in turn is associated with increased mortality.[72]

Patient financial costs are not limited to the direct cost of the drug itself. Some anti-neoplastic medications have indirect costs as well. For example, patients on trastuzumab undergo regular echocardiograms to monitor heart function,[73] and men with prostate cancer receiving androgen deprivation therapy need bone mineral density monitoring with dual-energy x-ray absorptiometry (DEXA) scans[74] and consideration of costly bone modifying agents (e.g. denosumab) if osteopenia or osteoporosis develop. These downstream costs may have financial implications not only for patients but also for the health care system.

In addition to financial concerns, the overuse of medications in cancer may have clinical harms. These harms include both acute side effects and toxicities and downstream (i.e. long term) physical or psychological complications; these harms are consequences of receiving the medication regardless of its appropriateness. Acute medication toxicities of cancer drugs are common and sometimes life-threatening. For example, inappropriate chemotherapy use in early stage colon cancer can cause avoidable myelosuppression which can predispose to a life-threatening infection. In addition, many cancer medications cause side effects such as fatigue, which though not life-threatening can substantially impact quality of life. Beyond the acute setting, long term harms of overused medications are common and may be severe as well; for example, inappropriate oxaliplatin use for early stage colon cancer can cause

permanent peripheral neuropathy, and other commonly used chemotherapies can cause potentially fatal secondary leukemias.[75]

Despite their importance for patients, few studies document clinical harms of overuse.[13] Only one of the 30 studies we found quantified the clinical harms of the overused medication.[61] In this study, inappropriate trastuzumab use in patients with breast cancer led to increased rates of heart failure (hazard ratio 1·6) compared to chemotherapy alone. Psychological implications of medication overuse are poorly studied but might have special importance in cancer patients,[76] since over 40% of cancer patients have at least sub-clinical depression after diagnosis and even more suffer from anxiety,[77] both of which may be exacerbated by medication overuse.

Finally, overuse of medications in cancer can have important opportunity costs for patients, clinicians, and the healthcare system. For patients, non-beneficial medications may occupy valuable time,[76] particularly in the case of intravenous medications which involve spending time in waiting rooms and infusion suites instead of at home or with family. Inappropriate treatment might also replace more beneficial treatment, or in some situations forestall a shift in focus towards symptom control or psychosocial needs. For physicians, inappropriate treatment for one patient may divert time and attention from other patients with pressing clinical needs. And finally, in the context of important disparities in cancer care outcomes[78–81] that relate at least in part to unequal distribution of scarce resources, overuse represents squandered resources with negative returns.

Evidence of Overuse: “What We Don’t Know”

There are large gaps in the literature evaluating medication overuse in oncology. First, few studies have evaluated medication overuse in LMICs, where safety concerns for oncology drugs are higher[82] and where the cost implications of unnecessary drugs may be dire in the context of limited budgets. Second, few high-cost antineoplastic agents have been studied; pemetrexed, for which geographic variations in use were documented, was the most expensive chemotherapy agent for which overuse was evaluated.[49] In particular, despite widespread enthusiasm about their potential to dramatically improve clinical outcomes[83] and near-universal concern about exorbitant cost, we found no studies investigating overuse of immunotherapeutic agents. Similarly, we found no studies of newer specialty pharmaceuticals despite findings that as of 2012 all were initially priced in the US at greater than $60,000 for one year of treatment.[84] Beyond cost, the potential long-term harms of these agents are unclear but may be serious,[85–88] so their overuse may have important clinical as well as financial implications. The lack of study of overuse of newer high-cost antineoplastic likely relates to the relatively recent release of these medications and may emerge soon.

We also found no studies of a potentially common example of medication overuse in oncology. Polychemotherapy has not been shown to improve survival over sequential single agent chemotherapy in patients with advanced breast cancer but it worsens quality of life.[89] While international guidelines recommend sequential single agent chemotherapy in this setting[90] and ASCO’s Choosing Wisely list[18] called attention to the issue by including a

recommendation against unnecessary combination chemotherapy, we found no studies investigating the overuse of polychemotherapy in metastatic breast cancer. Future studies should focus on particularly costly or particularly common potential examples of medication overuse.

Mitigating Overuse in Oncology

The substantial potential financial and clinical harms of medication overuse in oncology suggest the need for coordinated efforts to reduce overuse. However, reducing overuse is not a simple task.[91] Several societal-level interventions to reduce overuse have been implemented, including the ABIM Foundation's Choosing Wisely Campaign, which began in the US but quickly spread to Canada, Australia, Japan, and much of Europe.[92] Despite enthusiasm, the impact of Choosing Wisely thus far has been modest[93] and high-level campaigns are likely to be inadequate for reducing overuse. Given the varied drivers of overuse in different settings, local efforts are likely needed. Among the 30 studies we found documenting medication overuse in oncology, four tested interventions to reduce overuse, of which all were conducted at the institution level. Three studies found reductions in antineoplastic medication overuse for colorectal cancer,[52] lung cancer,[53] and thyroid cancer[94] after pathway implementation. A single study evaluated a quality improvement initiative: Patil et al[30] found that anti-emetic overuse could be reduced at a single institution through enhanced clinician education and peer review by colleague physicians of all anti-emetic prescribing. Further study of these types of approaches is needed to inform broad efforts to reduce overuse.

Concluding Remarks

The existing evidence regarding medication overuse in cancer is limited to a few medications, with no studies of many of the most toxic or most expensive medications. In addition, there is a paucity of studies investigating overuse in LMICs, and little data describing the financial, psychological, and physical harms of medication overuse. To protect patients and healthcare systems across the globe, more research is needed to better quantify rates of overuse, understand implications of overuse, and test ways to reduce inappropriate medication use in cancer.

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Table 1.

Types of evidence for determining overuse of medications.

Type of evidence	Description
Direct	Directly compares drug utilization to accepted standard to define inappropriate use at the individual patient level.
Indirect: Variation	Large unexplained variation in drug utilization across prescribers or settings reflects overuse among high users.
Indirect: Intervention effect	Reduction in drug utilization after intervention implies previous overuse.

This table is adapted from concepts described in Brownlee et al.[1]

Table 2.

Overuse of supportive medications in oncology.

Author, Year	Country, Patient population	Type of Evidence	Sample Size (patients)	Findings
Anti-Emetics				
Encinosa, 2017[2]	US, adults starting chemotherapy	Direct	678,220	Overuse of any anti-emetic agent in 24·1% of patients, varying by emetogenic risk group; temporary improvement after Choosing Wisely.
Burmeister, 2012[3]	Switzerland, adults starting chemotherapy	Direct	54	Overuse of serotonin receptor antagonist in 72·2% of patients with low emetogenic chemotherapy.
Okuyama, 2017[4]	Japan, adults starting chemotherapy	Direct	8,545	Overuse of serotonin receptor antagonists and corticosteroids in 47.8% and 2.8% of patients receiving chemotherapy with minimal and low emetic risk, respectively.
Zong, 2016[5]	China, adults receiving chemotherapy	Direct	14,548	Approximately 20% of patients received dual serotonin receptor antagonists or corticosteroids.
Franca, 2015[6]	Brazil, adults starting chemotherapy	Direct	105	Above recommended anti-emetic agent doses in 45·7% of patients.
Patil, 2017[7]	India, adults receiving chemotherapy	Direct/Indirect: intervention	1,211	Overuse of any anti-emetic agent in 68·3% of patients; this was decreased to 41.3% after a quality improvement intervention.
Growth Factor Support				
Wright, 2013[8]	US, adults with solid tumors admitted with FN	Direct	25,231	Inappropriate prophylactic filgrastim or pegfilgrastim use in 62·1% of patients at low-risk for FN.
Ramsey, 2010[9]	US (Washington State) adults with breast, colon, or NSCLC	Direct	~3.7 million	Prophylactic filgrastim or pegfilgrastim overuse in low-risk chemotherapy regimens in breast cancer (10%), colon cancer (7%), and NSCLC (21%) patients.
Waters, 2013[10]	US adults who received chemotherapy	Direct	292	Authors classified 46% of pegfilgrastim doses as avoidable.
Potosky, 2011[11]	US, adults receiving chemotherapy for lung or colorectal cancer	Direct	1,849	96% of GCSF use occurred outside ASCO and NCCN guideline recommendations.
Hrushesky, 2014[12] (ASCO abstract)	US, Southeastern region	Direct	17,000	GCSF overuse in 40% of cases in which patients received low-risk chemotherapy.

Author, Year	Country, Patient population	Type of Evidence	Sample Size (patients)	Findings
Wright, 2011[13]	US, adults with breast, lung, or colorectal cancer	Direct	21,091	Off-label ESA use in 13·6% of patients.
Du, 2005[14]	US, adults with breast cancer receiving chemotherapy	Indirect: variation	5,843	Geographic variation in growth factor use: 10·6% −22·9% for filgrastim; 2·7%−12·8% for epoetin.
Rajan, 2017[15]	US, adults with lung cancer	Indirect: variation	80,940	Geographic variation in growth factor use: 26·2% −43·1% for any GCSF; 29·9%−51·6% for epoetin or darbepoetin.
Zhang, 2014[16]	US, adults with colorectal cancer	Indirect: variation	50,768	Geographical variation in growth factor use: 8·6% −23·5% for filgrastim, pegfilgrastim, or sargramostim; 14·9% −35·7% for epoetin or darbepoetin.
Clough, 2015[17]	US, adults with cancer receiving >$200 in chemotherapy payments	Indirect: variation	397,644	Found approximately 2·5x higher spending on pegfilgrastim and darbepoetin in practices with the highest overall spending quartile compared to those in the lowest.

Medications in table listed to the maximum specificity available in original source. Abbreviations: FN = fever and neutropenia; NSCLC = non-small cell lung cancer; GCSF = granulocyte colony stimulating factor; ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESA = erythropoiesis stimulating agent.

Table 3.

Overuse of anti-neoplastic medications in oncology.

Author, Year	Country, Patient population	Type of Evidence	Sample Size (patients)	Findings
Chemotherapy				
Landrum, 2008[18]	US, adults with stage I colorectal cancer	Direct	10,998	Overuse of chemotherapy ranged from 3·1% (for low spending areas) to 6·3% (in highest spending areas).
Landrum, 2008[18]	US, adults with stage II colorectal cancer	Indirect: variation	16,371	Geographic variation in chemotherapy, range 18%−22·6%.
Hoverman, 2011[19]	US, adults with colorectal cancer	Indirect: intervention	910	Patients treated on pathway had lower chemotherapy costs (adjuvant setting: $60,787 to $22,564; metastatic setting: $65,358 to $41,894). Three year DFS and 1 year OS were higher for patients on pathway.
Clough, 2015[17]	US, adults with cancer receiving >$200 in chemotherapy payments	Indirect: variation	397,644	Approximately 1·7x higher spending on pemetrexed in practices with the highest overall spending quartile compared to those in the lowest.
Jackman, 2017[20]	US (DFCI), adults with stage IV NSCLC	Indirect: intervention	370	Pathway reduced anti-neoplastic medication spending from mean $44,237 to $31,846.
Mahar, 2014[21]	Canada, adults with surgically resected NSCLC	Indirect: variation	3,354	Proportion of patients receiving adjuvant cisplatin/vinorelbine varied from 20 to 43% by geographical region.
Jacobson, 2010[22]	US, adults with newly diagnosed lung cancer	Indirect: intervention	222,478	Prescribing rates of carboplatin decreased from 55·9% to 53·7%, paclitaxel decreased from 30·0% to 26·2%, and docetaxel increased from 9·2% to 9·7% Medicare chemotherapy reimbursement rate change.
Guy, 2015[23]	US (Rural Georgia), adults with early stage breast cancer	Direct	868	Overuse rates of endocrine therapy, chemotherapy, and radiation therapy ranged 11·5%−18·2%.*
Biologic Agents				
Clough, 2015[17]	US, adults with cancer receiving >$200 in chemotherapy payments	Indirect: variation	397,644	Approximately 2·2x higher spending on bevacizumab and a 1·7x higher spending on cetuximab in practices with the highest overall spending quartile

Author, Year	Country, Patient population	Type of Evidence	Sample Size (patients)	Findings
				compared to those in the lowest.
Haas, 2011[24]	US, adults with localized breast cancer.	Direct	775	Among women without a positive HER2 test, 3·9% still received trastuzumab.
Tina Shih, 2014[25]	US, elderly adults with breast cancer who received trastuzumab	Direct	2,984	Among women who received trastuzumab, 4·7% had no documentation of HER2 testing. Use was associated with increased HF with no survival benefit.
Androgen Deprivation Therapy (ADT)				
Ellis, 2016[26]	US, adults with localized prostate cancer	Direct	12,943	Goserelin, leuprolide, or triptorelin overuse in 21% of patients, decreased to 13·6% after Medicare Modernization Act decreased reimbursement. Overuse higher in solo practice settings.
Quek, 2014[27]	US, adults with T1-T2 clinical stage, low-intermediate grade prostate cancer	Direct	12,255	Non-evidence based GnRH agonist use in 32% of patients with higher use in patients treated by urologists with no medical school affiliations.
Shahinian, 2015[28]	US, adults with localized, low risk, prostate cancer	Direct and Indirect: intervention	27,169	Rate of inappropriate ADT (GnRH agonists or orchiectomy) use 44% in 2000, decreased to 31% in 2007 after 2005 reimbursement change.
Swisher-McClure, 2012[29]	US, adults with localized, low risk, prostate cancer receiving radiation therapy.	Indirect: variation	2,184	Geographic variation in use of GnRH agonists or orchiectomy in low risk patients in combination with radiation therapy (Range 14% to 48%).
Radioactive Iodine (RAI)				
Sacks, 2015[30]	US, adults with differentiated stage 1 thyroid cancer.	Direct	444	Reduction in RAI treatment for stage I DTC from ~50% to 20% between 1998 and 2011 at CSMC after guideline implementation, compared to stable national usage rates of >50% during same timeframe.
Goffredo, 2016[31]	US, adults with papillary thyroid cancer <1cm	Direct	60,586	23·3% of patients were inappropriately treated with RAI.

Medications in table listed to the maximum specificity available in original source. Abbreviations: DFS = disease free survival; OS = overall survival; HER2 = human epidermal growth factor receptor 2; HF = heart failure; GnRH = gonadotropin releasing hormone agonist; DTC = differentiated thyroid cancer; CSMS = Cedars-Sinai Medical Center.

*Numbers not published in main paper, so based on author communication and reported in Baxi et al.[32]

Table 4.

Cost per dose of medication in U.S. Dollars (USD).

Drug	Dose Description	US	UK	Canada	Denmark
Palonosetron	250 mcg IV dose	$220.51	$0.12	N/A	$53.35
Ondansetron	4 mg oral dose	$0.14-$6.50 *	$1,018.97	$9.18	$0.20
Bevacizumab	5 mg/kg dose for 70 kg person	$2,619.47	$265.29	N/A	$1,107.62
Epoetin Alfa	40,000 units	$550.40	$1,026.43	$413.37	N/A
Trastuzumab	6 mg/kg dose for 70 kg person	$4,058.50	N/A	N/A	$1,148.14
Leuprolide Acetate	7.5 mg dose	$192.96	$823.48	$14.72	N/A
Pegfilgrastim	6 mg dose	$4,247.25	$63.23	N/A	$989.78
Filgrastim	300 mcg dose	$302.40	$0.00	$125.63	$81.54

Prices are based on the lowest cost brand drug, or generic drugs when available. The price per smallest package size available was used to minimize effects of reference prices that don't consider package size. The source for the UK was the MIMS database, because many of these drugs aren't available on the British National Formulary. The source for Denmark was the ministry of health's figures for prescription drugs. The source for Canada was Quebec's RAMQ database. All prices were converted to USD with the Treasury Department's for each country in June 2017.

* Range of ondansetron price reflects differential payments between Medicare Parts B and D.