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Title:

Pharmaceutical payments to certified oncology specialists in Japan in 2016: a retrospective observational study

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Abstract

Objective: This study aimed to elucidate the characteristics of payments from pharmaceutical companies to oncology specialists in Japan, whether the

payment was made for promotion, and whether there are specific rules to cover Conflict of Interest (COI) matters among the oncology specialists.

Design, Setting, and Participants: The participants were oncology specialists certified by the Japanese Society of Medical Oncology (JSMO) up to 2016. We retrospectively extracted 2016 payment data reported by 71 Japanese pharmaceutical companies.

Outcome measures: We made descriptive analyses for payments to the individual specialists, made generalized linear models to estimate factors associated with higher value payments, made a Sankey diagram to illustrate the payment flow from the companies to oncology subspecialties, analyzed oncology drugs with the annual sales of ¥5 billion [$44,424,500] or above, and examined the JSMO policy for disclosing COIs.

Results: The total and mean monetary value of payments from pharmaceutical companies was ¥598,286,743 [$5,315,718], and ¥553,457 [$4,917] (standard deviation ¥1,264,398 [$11,234]), respectively. Of the 1081 specialists sampled,

779 (72.1%) received a payment. Of this total, 147 (13.6%) receiving a payment of at least ¥100,000 [$8,918] received 72.5% of the total payment (¥433,622,808 [$3,852,695]). In the generalized linear models, working for a university hospital (IRR=2.43, 95% CI=1.78–3.31) was a key factor associated with larger monetary payments. the payment was likely to made toward the specialties with high-income drugs, though its tendency differed between companies. Oncologists were not required to disclose any COIs related to their work.

Conclusion: Substantial financial relationships were observed between pharmaceutical companies and oncology specialists, but their extents varied significantly between individuals. The oncology specialists were not required to disclose any COIs related to their work.

Keywords: conflicts of interest; oncology specialist; Japan; industry payment; Japanese Society of Medical Oncology

Article summary (Strengths and limitations of this study):

- ✓ To the best of our knowledge, this study is the first to investigate individual payment value of the certified oncology specialists both in Japan and worldwide.
- ✓ The authors independently organized the payment data published by the major pharmaceutical companies, and created a single uniform database for the payment.
- ✓ This study only covered the payment data in 2016, which hampered a longitudinal analysis of the type and value of the payment among the oncology specialists.

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Introduction

Pharmaceutical policy-making and medical practice is riddled with opportunities for exploitation, especially given the huge amounts of money involved.[1-3] From the 1950s, the main business model of the pharmaceutical industry was the production of low-price drugs to treat diseases and conditions that were primarily chronic (e.g. hypertension and diabetes).[4-6] With ageing populations, pollution,

poor or excessive nutrition and the like cancer became an ever-increasing and major problem.[7] The pharmaceutical industry therefore adopted a new business model, discovery and development of anticancer agents which could be sold at extremely high price, but usually for short treatment durations.[1-3] This guaranteed a hefty profit in a short timeframe, provided that the drugs would be prescribed and used, while imposing an extraordinarily high cost to the patients.[1-3 8] Indeed, a single administration of tisagenlecleucel, a recently-approved chimeric antigen receptor T-cell immunotherapy manufactured by Novartis Pharma, reportedly costs $475,000.[9]

Physicians remain paramount decision-makers on the demand-side of the pharmaceutical market. Even subtle financial interactions between physicians and a pharmaceutical company are known to affect their prescribing behavior,[10-15] and could encourage irrational or preferential use of a company's drug. Unsurprisingly, oncologists have recently become primary targets for approaches from companies with high-cost anticancer products to sell. Indeed, significant financial relationships between such companies and the authors of the Clinical Practice Guideline (CPG) issued by the National Comprehensive

Cancer Networks (NCCN) have been reported.[16] Given these murky circumstances, there has been a growing need for intervention, in the form of policy implementation and education about the implications of these interactions to help protect doctors, patients, institutions and the companies themselves.[12-15] Consequently, medical and governmental facilities worldwide are considering guidelines, self-regulation and legislative checks to help control the relationship between physicians and the pharmaceutical industry, exemplified by the USA's Physician Payments Sunshine Act, enacted in 2010.[17 18]

Although Japan has the third largest pharmaceutical market, with annual pharmaceutical sales of $76 billion in 2017,[19] its overall scale has been declining at approximately 2% annually.[20] To maintain sales in these competitive and tightening markets, forceful advertisement of high-price products, namely novel oncology drugs, has become increasingly important for pharmaceutical companies. Indeed, sales of oncology drugs have recently been rising in Japan, exceeding ¥1 trillion [$8.9 billion] for the first time in 2016.[21] Furthermore, sales are predicted to increase 1.5–fold in the next decade with the increasing application of immunotherapy in clinical practice.[21] It would be reasonable to

assume that pharmaceutical companies will increasingly deploy marketing measures and incentives targeting oncology specialists for the immediate and foreseeable future.

In Japan, the Japan Pharmaceutical Manufacturers Association (JPMA) has made details of pharmaceutical company payments publicly available since fiscal year 2013.[22] The aim was to improve the transparency of linkages between pharmaceutical companies and physicians, as in the USA's Physician Payments Sunshine Act,[17 18] the transparency surrounding payment disclosures in Japan being traditionally very poor, with examination of company/physicians links and payments in a meaningful way proving almost impossible. Furthermore, little was known about regulations concerning oncologists having to declare details with respect to Conflicts of Interest (COIs) that could affect their work.

The aims of the current study were: 1) to understand and evaluate the characteristics and distributions of financial payments made by pharmaceutical companies to oncology specialists: 2) to examine a well-accepted belief that pharmaceutical companies make payments to promote their products; and 3) to

elucidate whether Japanese oncology specialists are obliged in any way to disclose their COIs.

Methods

Study setting and participants

We included all oncology specialists certified by the Japanese Society of Medical Oncology (JSMO) as of the beginning of April 1, 2016. The JSMO, with 9,154 members in 2017, is the largest professional medical society in the oncology field in Japan. The JSMO began operating a specialty recording system for members in 2004. In general, Japanese certified oncologists have strong discretionary power with respect to their prescribing of oncology drugs, as, in the past, only these physicians were allowed to prescribe specific agents, such as nivolumab and gefitinib.

Sources of Payment Data

We collected payment data, as published by all 71 companies that belonged to the JPMA. For most eligible companies, the 2016 data was the most recent, with previous payment data being unavailable. The companies included in this study,

plus the starting and ending dates of their payment data, are listed in Supplementary Material 1.

We obtained each company's data and organized them into a unified single database as follows; first, because no data was published as a spreadsheet, data with character codes was converted into a spreadsheet format. Second, data with no character code was converted into text files using an Optical Character Reader. Third, when data was protected against facsimile or reproduction, we used FullShot10 software (Inbit, CA, USA) to scan photos of the data and converted the data into text files. Finally, we confirmed the accuracy of the organized data by comparing it with the original data. The database included physicians' names, their main institutions, payments received, the form of the payments, and the total amount of payments. The form of payment was categorized into three types; payment for speaking, payment for writing, and consulting fees.

Data collection

We examined payment data for all oncology specialists included in this study. Further, we determined their main working institution and region, along with the year of their certification from the JSMO website. We further extracted the subspecialties (respiratory, gastroenterology, hematology, breast, etc.) of all individuals who received a payment of ¥1 million [$8,885] or above from any pharmaceutical company, collating data from institutional websites using an internet search engine (Google). In general, ¥1 million [$8,885] is approximately 25% of the median annual income of a Japanese citizen.[23] In addition, we attempted find any COI policy from the JSMO website.

Data analysis

To examine the characteristics and distributions of payments, we performed descriptive analyses of the data on an individual oncology specialist and pharmaceutical company basis. We then specifically summarized the characteristics of oncology specialists receiving a total payment of ¥1 million [$8,885] or above. Using a multivariate negative binomial regression model, we subsequently examined possible factors associated with the monetary value of the payment to the individual oncologists, using working institutions, working

regions, and year of experience after the board certification as covariates. The payment data was rounded off as a unit of ¥1 million [$8,885]. Further, to assess the effects of the subspecialty on the value of the payment, using a zero-truncated negative binomial model, we repeated the analysis among those receiving payments of ¥1 million [$8,885] or above. Second, to confirm whether the payment was made for promotional purposes, we created a Sankey diagram among the specialists in this cohort to illustrate the distribution of the payment to each subspecialty on an individual company basis. The Sankey diagram is a flow diagram, where band width proportionally represents the flow quantity.[24] Payment values from individual companies, according to subspecialty, are depicted in the bands in the diagram, width being proportional to the total amount of the payment. In addition, to see whether the payment was linked to any specific oncology drugs, we examined such drugs with annual Japanese domestic sales of ¥5 billion [$44,424,500] or above, and if each drug was covered in the Japanese National Health Insurance scheme in 2016. We converted Japanese yen (¥) to US dollars ($) using the October 21, 2018 exchange rate of ¥113 yen per US$1.

Ethics approval

This study was approved by the Institutional Review Board of Medical Governance Research Institute (MEGRI) on 16 May 2018.

Patient and Public Involvement

The present study is a retrospective analysis of the existing database, and we did not include the patients and other population in particular in the development of the study design.

Role of the funding source

The funders – Ain Pharmaciez Inc. and Waseda Chronicle made no contribution whatsoever to either the design of the study, the work carried out or the interpretation of the study findings.

Results

Table 1 summarizes the details of certified oncology specialists and payments from Japanese pharmaceutical firms. Of 1081 eligible certified oncology

specialists, 315 (29.1%), 142 (13.1%), and 407 (37.7%) worked for university hospitals, cancer hospitals, and other general hospitals, respectively.

The total monetary value of the payments made was ¥598,286,743 [$5,315,718], entailing 7,445 payments. The mean and median monetary value of an individual payment was ¥553,457 [$4,917] (standard deviation (SD) ¥1,264,398 [$11,234]) and ¥122,507 [$1,088] (interquartile range (IQR) ¥ 0–445,480 [$0–3,958]), respectively. Similarly, the mean and median figure for the number of individual payments was 7 (SD 13) and 2 (IQR 0–7), respectively. The number of oncology specialists receiving any payment was 779 (72.1%). Of the 1081 participants, 147 (13.6%) received payments totaling ¥1 million [$8,885] or more. while 20 (1.9%) received ¥5 million [$44,425] or above. Only 3 (0.2%) received ¥10 million [$88,849] or above.

A summary of payments of 56 companies which made any payment to the oncologists s is shown in Table 2. The Chugai Pharmaceutical Co. Ltd., a subsidiary of F. Hoffmann-La Roche Ltd, made the largest total payment of ¥103,727,395 [$921,608], while Toyama Chemical Co., Ltd. paid the lowest

(¥33,410 [$297]). The mean and median monetary value among the companies was ¥10,877,941 [$96,649] (SD ¥19,041,596 [$169,183]) and ¥2,099,790 [$18,656] (IQR ¥423,206–15,207,296 [$3,760–135,115]), respectively.

Table 3 summarizes the characteristics of specialists receiving a total payment of ¥1 million [$8,885] and above. Overall, 50.3% worked for university hospitals, and 19.0% were certified within the last five years (2012–2016). The top three subspecialties attracting payments were respiratory (56 (38.1%)), gastroenterology (36 (24.5%)), and hematology (27 (18.4%)). The total monetary value and count was ¥433,622,808 [$3,852,695] and 4,606, respectively accounting for 72.5% and 61.9% of the totals, with respiratory attracting (¥177,274,111 [$1,575,062] (40.9%)), gastroenterology (¥100,424,612 [$892,262] (23.2%)) and hematology (¥81,649,310 [$725,446] (18.8%)).

Table 4 displays findings of the multivariate regression analyses for the monetary value of payments. Oncologists with longer experience after board certification (incidence rate ratio (IRR)=1.30, 95% CI=1.23–1.37, p<0.001) and those working for university hospitals (IRR=2.43, 95% CI=1.78–3.31, p<0.001)

were significantly more likely to receive larger payments compared with their counterparts. Similar trends were observed for those with payment values of ¥1 million [$8,885] or above. Those working in the respiratory subspecialty were likely to receive higher payments compared with all others, although this trend was not statistically significant.

Figure 1 displays payment distributions to each subspecialty on an individual company basis. Details of the payments are provided in Supplementary Material 2. Further, in Table 5, we summarize the list of oncology drugs with Japanese domestic sales of ¥5 billion [$44,424,500] or more. Chugai Pharmaceutical Co., Ltd. made the largest subspecialty payment of ¥74,542,676 [$662,304], and the top four subspecialties were respiratory (¥25,061,169 [$222,666], 33.6%), gastroenterology (¥24,264,112 [$215,584], 32.6%), hematology (¥14,242,968 [$126,547], 19.1%), and breast (¥8,958,305 [79,594]. 12.0%). The Chugai company manufactured eight oncology drugs with annual sales of ¥5 billion [$44,424,500] or more (Table 5), and three, four, one, and five drugs were respectively covered in under the National Health Insurance scheme in respiratory, gastroenterology, hematology, and breast subspecialties. Nivolumab,

manufactured by the Ono Pharmaceutical Co., Ltd., and used in respiratory and dermatology subspecialties, had the largest domestic sales in 2016 (¥103.9 billion [$923,141,110]). The total monetary value of the company's payments was ¥36,906,340 [$327,909] (representing third place in the payment table), of which ¥24,623,912 [$218,781] (66.7%) was specifically distributed to the respiratory subspecialty.

The COI policy of the JSMO does not mention how oncology specialists should disclose their financial relationships with pharmaceutical industry enterprises and they do not have to report any financial relationships to the JSMO or publicly.

Discussion

In this study, approximately ¥600 million [$5,330,940] was paid by Japanese pharmaceutical companies to around 70% of the 1081 certified oncology specialists, all of whom were under no obligation to disclose the payments. Payments were concentrated on specific targets, notably oncologists working for university hospitals.

Compared to past studies, the proportion of certified oncologists receiving payments was larger than for general physicians in the US (48.0%)[25] and Japan (33.3%).[26] The proportion was only slightly smaller than that of NCCN oncology CPG authors in the US (86.4%).[16] Although the mean value of payments in our study was approximately half of that of the CPG authors ($4,917 vs.$10,011), a simple comparison is not valid as our analysis did not include stock ownership, investment interest, or payments from medical device companies.[25] The CPG authors strongly influence oncology practice both in the US and internationally,[27] by recommending treatment algorithms. They thus become prime targets for influence from pharmaceutical companies selling anticancer products. It is clear that Japanese pharmaceutical companies with similar anticancer interests would target oncology specialists and attempt to boost the sales and use of their specific products.

We observed a large disparity in payments to specialists. Those receiving ¥1 million or more accounted for 13.6% of the total participating but received 72.5% of the total paid. Companies appear to have consciously targeted their funds to

maximize promotion of their products, but not as expected. Oncologists working for university hospitals were more likely to receive a larger value payment. But in Japanese medical circles, cancer centers are generally more likely to treat more cancer patients compared to university hospitals. Indeed, cancer centers top the nationwide ratings for treatments in most of the common cancers, including lung, colon, gastric, and breast cancer.[28] In contrast, university hospitals are regarded as symbols of academic excellence and authority, and medical school professors traditionally have a strong influence on both physicians and medical practice in their field of expertise. Thus, our findings suggest that Japanese pharmaceutical companies have placed greater emphasis on expertise and authority, compared with clinical experience, in the selection of targets for their promotional activities.

We found that the respiratory subspecialty attracted the greatest financial outlay. In Japan, this field covers a large patient volume and involves multiple novel oncology drugs, such as nivolumab (Ono Pharmaceutical Co., Ltd, (approved 2015)), pembrolizumab (MSD K.K., (2016)), alectinib (Chugai Pharmaceutical Co., Ltd., (2014)), osimertinib (AstraZeneca plc, (2016)), ramcirumab (Eli Lilly

Japan K.K., (2016)), and afanitinib (Nippon Boehringer Ingelheim Co., Ltd., (2016)), all for non-small cell lung cancer. As such, for the pharmaceutical companies, this field is a critical yet highly competitive target in any strategy to maximize the cost-effectiveness of their promotional endeavors.

The examples of Chugai Pharmaceutical and Ono Pharmaceutical confirm the belief that there is an association between the value and destination of payments dependent on the products the companies in question manufacture. AstraZeneca may, from our findings, be an exception to this rule. While it made the second largest total payments to physicians with a known subspecialty (¥43,836,859 [$389,486]), it did not have any oncology drugs providing a high income. However, it does sell an immunotherapy agent dulvalumab, which was covered by the National Health Insurance scheme for treating non-small cell lung cancer in 2018. Thus, it is reasonable to assume that funds were allocated to promote their forthcoming product and engage and incentivize key individuals for future relationships. Indeed, 86% of the company's payment was allocated to the respiratory subspecialty.

Surprisingly, there is no clear rule for COI disclosure among Japanese oncology specialists. As we have demonstrated, there is an emphatic financial relationship between pharmaceutical companies and oncologists, which to many would appear unhealthy or of a somewhat dubious nature. It is true that the receipt of the abovementioned payments in Japan is not illegal, as they are supposedly given as remuneration for lectures, writing and consultations. However, we believe that there is an ethical problem inherent in such relationships, given that this practice could have developed to possibly end up expanding the profit of pharmaceutical companies, rather than promoting the health and well-being of patients. Indeed, even a subtle but reputable financial relationship with the industry, such as collaborating in a field trial, could bias the physicians' prescription patterns in a manner that benefits the companies.[10-15] Oncologists in Japan handle extraordinary and very potent life-saving drugs, and have a degree of autonomy in their prescribing actions. Their decisions substantially influence the treatment and outcome for their patients, as well as having significant economic impact due to the high cost of anticancer medications.[1-3] It would therefore appear sensible to have rigorous regulations to cover the open and accessible reporting of any financial dealings between physicians and

pharmaceutical companies so as to avoid any potential nefarious or underhand behavior or undue pressure on physicians to alter their usual treatment practices. Indeed, it is possible that these highly-questionable arrangements may have contributed to the multiple cases of scientific misconduct that have recently been reported in Japan. The most infamous case was when employee misconduct was discovered in a series of clinical trials for Valsartan, an antihypertensive medication manufactured by Novartis Pharma, leading to a retraction of the associated academic papers.[29 30] A breast cancer clinical trial (CREATE-X trial) with a questionable pharmaceutical payment has also been identified.[31 32]

To prevent similar cases in future, we call for the implementation of a transparent, independent mechanism that would enable a comprehensive assessment of any and all payments being made by any pharmaceutical company to any individual physician or, for that matter, medical institution where the company's products may be used, and not just with respect to oncology. New schemes, such as the US's Open Payments, may prove successful but it is too soon to know.[33] The Disclosure UK mechanism may not prove so useful as it is voluntary. Additionally, given that such mechanisms allow for direct

comparison between what is allegedly paid and what is allegedly received, it will necessitate a fair, equitable and timely mechanism for dispute settlement, probably involving the use of third parties. [32]

Conclusion

Japanese certified oncologists receive financial payments direct from pharmaceutical companies, usually from those active in the specialist field of the physician in question. This raises several queries with regard to ethical, medical and possibly legal issues. The value and speciality targets of the payments varied substantially which also raises yet more questions as to why. We believe that the lessons learned from our analyses should be shared among the global medical community to put in place safeguards to prevent undue and unethical inducements from the pharmaceutical industry and to help protect physicians from outside influences. It is essential to establish a robust, comprehensive and binding system for identifying and avoiding any and all potential conflicts of interest, of any nature, involving physicians or other medical professionals, both in Japan and internationally.

Author contributors:

A.O acquired, had full access to and control of all data, and oversaw all data analyses.

All authors were involved in the study concept and design:

All authors were involved in the analysis, interpretation of results and formation of conclusions

A.O. and A.C drafted the manuscript.

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Conflict of interest statement

A.O and T.T receive personal fees from Medical Network Systems (MNES Inc.); H.S has received an honorarium from TAIHO Pharmaceutical Co., Ltd. for research outside the purview of work carried out during this study. All other authors declare no conflict of interests.

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Data sharing statement:

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Figure legends:

Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band colour represents the payment destination

specialties. Due to space limitations, names of companies with payment values of less than ¥10 million [$8,885] have been omitted.

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Table 1. Characteristics of oncology specialists and pharmaceutical payment received by individual doctors.

Variable		
1. Characteristics of oncology specialists (N=1081)		
Working institutions	(N (%))	
University hospitals		315 (29.1)
Cancer hospitals		142 (13.1)
Other general hospitals		407 (37.7)
Undisclosed		217 (20.1)
Working regions	(N, %)	
Hokkaido		52 (4.8)
Tohoku		54 (5.0)
Kanto		311 (28.8)
Chubu		191 (19.4)
Kinki		210 (19.4)
Chugoku		84 (7.8)
Shikoku		44 (4.1)
Kyushu		135 (12.5)
Year of certification	(N, %)	
2006		45 (4.2)
2007		77 (7.1)
2008		72 (6.7)
2009		98 (9.1)
2010		133 (12.3)
2011		130 (12.0)
2012		124 (11.5)
2013		143 (13.2)
2014		98 (9.1)
2015		85 (7.9)
2016		76 (7.0)
2. Characteristics of pharmaceutical company payments		
Monetary value of payment		
Total payment (¥)		598,286,743

Mean monetary value (¥, standard deviation)		553,457 (1,264,398)
Median monetary value (¥, Interquartile range)		122,507 (0–445,480)
Number of payments		
Total count		7,445
Mean count (standard deviation)		7 (13)
Median count (Interquartile range)		2 (0–7)
Number of oncology specialists with payment	(N, %)	(N=1081)
Any		779 (72.1)
¥1 million or above		147 (13.6)
¥5 million or above		20 (1.9)
¥10 million or above		3 (0.2)

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572 **Table 2. Companies making a payment to oncology specialists**

Company name	Monetary Value (¥)
Chugai Pharmaceutical Co., Ltd.	103,727,395
AstraZeneca plc	53,142,723
Taiho Pharmaceutical Co., Ltd.	51,135,629
Ono Pharmaceutical Co., Ltd.	48,655,875
Eli Lilly Japan K.K.	44,825,340
Bristol-Myers Squibb	33,443,966
Takeda Pharmaceutical Co., Ltd.	28,280,960
Novartis International AG	26,813,551
Nippon Boehringer Ingelheim Co., Ltd.	26,071,503
Kyowa Hakko Kirin Co., Ltd.	21,861,357
Pfizer Inc.	20,606,008
Merck Serono	16,411,157
Eisai Co., Ltd.	16,342,547
Celgene Corporation	15,207,296
Mitsubishi Tanabe Pharma Corporation	11,970,589
Daiichi Sankyo Co., Ltd.	8,827,786
Yakult Honsha Co., Ltd.	8,318,026
Janssen Pharmaceutical K.K.	7,667,831
MSD K.K.,	6,317,468
Sumitomo Dainippon Pharma Co., Ltd.	5,196,201
Bayer AG	4,562,759
Nippon Kayaku Co., Ltd.	3,579,218
Sanofi K.K.	3,535,000
Astellas Pharma Inc.	3,510,000
Nippon Shinyaku Co., Ltd.	3,129,497
Asahi Kasei Pharma Corporation	3,102,452
Otsuka Pharmaceutical Co., Ltd.	2,204,198
Teijin Pharma Limited	2,099,790
Shionogi & Co., Ltd.	2,052,088
Kyorin Pharmaceutical Co.,LTD.	1,948,969

Zeria Pharmaceutical Co., Ltd.	1,893,290
Tsumura & Co.	1,626,003
Kissei Pharmaceutical Co., Ltd.	1,236,210
Terumo Corporation	1,214,840
Meiji Seika	1,000,264
AbbVie GK	924,371
Sanwa Kagaku Kenkyusho Co., Ltd.	890,960
EA Pharma Co.,Ltd.	783,712
Kowa Company, Limited	590,262
Hisamitsu Pharmaceutical Co., Inc.	539,030
Novo Nordisk Pharma Ltd.	536,233
Aska Pharmaceutical Co., Ltd.	423,206
Nihon Pharmaceutical Co., Ltd.	311,836
Nippon Chemiphar Co., Ltd.	278,425
Kracie Pharmaceutical, Ltd.	268,112
Ayumi Pharmaceutical Corporation	226,864
Mylan N. V.	206,240
Torii Pharmaceutical Co., Ltd.	205,380
Kaken Pharmaceutical Co., Ltd.	111,370
GlaxoSmithKline plc	111,370
Minophagen Pharmaceutical Co., Ltd.	110,440
Mochida Pharmaceutical Co., Ltd.	89,096
Toray Industries, Inc.	77,080
Santen Pharmaceutical Co., Ltd.	51,560
Toyama Chemical Co., Ltd.	33,410

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Table 3. Characteristics of oncology specialists (receiving ¥1 million or more) and pharmaceutical company payments received by this group in 2016

Variable		
1. Characteristics of oncology specialists (N=147)		
Working institutions	(N, %)	
University hospitals		74 (50.3)
Cancer hospitals		40 (27.2)
Other general hospitals		24 (16.3)
Nondisclosed		9 (6.1)
Working regions	(N, %)	
Hokkaido		4 (2.7)
Tohoku		11 (7.5)
Kanto		51 (34.7)
Chubu		25 (17.0)
Kinki		29 (19.7)
Chugoku		8 (5.4)
Shikoku		5 (3.4)
Kyushu		14 (9.5)
Year of certification	(N, %)	
2006		22 (15.0)
2007		17 (11.6)
2008		20 (13.6)
2009		21 (14.3)
2010		23 (15.7)
2011		16 (10.9)
2012		9 (6.1)
2013		9 (6.1)
2014		5 (3.4)
2015		2 (1.4)
2016		3 (2.0)
Subspecialty of oncologists	(N, %)	
Respiratory		56 (38.1)

Gastroenterology	36 (24.5)
Hematology	27 (18.4)
Breast	16 (10.9)
Head and neck	2 (1.4)
Urology	1 (0.7)
Other	9 (6.1)
2. Characteristics of pharmaceutical payments of ¥1 million or more(N=147)	
Monetary value of payment	
Total value (¥)	433,622,808
Mean monetary value (¥, standard deviation)	2,949,815 (2,191,330)
Median monetary value (¥, Interquartile range)	2,179,352 (1,420,764–3,721,350)
Number of payments	
Total count	4,606
Mean count (standard deviation)	31 (21)
Median count (Interquartile range)	24 (17–39)
Monetary value of payment according to subspecialties (¥, %)	
Respiratory	177,274,111 (40.9)
Gastroenterology	100,424,612 (23.2)
Hematology	81,649,310 (18.8)
Breast	39,866,093 (9.2)
Urology	6,901,237 (1.6)
Head and neck	5,998,785 (1.4)
Other	21,508,660 (5.0)

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Table 4. Multivariate regression models for the monetary value of payment on an individual basis

Variable	All (N=1081) IRR (95% CI)	≥ ¥1 million (N=147) IRR (95% CI)
Year of experience after board certification	1.30 (1.23–1.37)***	1.09 (1.01–1.17)*
Institution		
Other type of medical institutions	Ref.	Ref.
University hospitals	2.43 (1.78–3.31)***	1.62 (1.16–2.27)**
Working region		
Kanto	Ref.	Ref.
Hokkaido	0.44 (0.18–1.08)	0.62 (0.25–1.52)
Tohoku	1.01 (0.56–1.81)	1.13 (0.67–1.90)
Chubu	0.65 (0.42–1.01)	0.67 (0.40–1.11)
Kinki	0.71 (0.47–1.06)	0.96 (0.62–1.50)
Chugoku	0.58 (0.26–1.30)	0.91 (0.37–2.22)
Shikoku	0.89 (0.43–1.87)	1.60 (0.86–2.99)
Kyushu	0.88 (0.54–1.44)	1.28 (0.71–2.32)
Subspecialty		
Respiratory		Ref.
Gastroenterology		0.72 (0.47–1.10)
Hematology		0.96 (0.67–1.38)
Breast		0.68 (0.39–1.20)
Other†		0.90 (0.42–1.92)

† Other subspecialties included Urology and Head and neck cancer. Due to the small number of physicians in these two subspecialties, they were included in the “other” category.

IRR=Incidence rate ratio, CI=Confidence interval

* <0.05, ** <0.01, *** <0.001

Table 5. List of oncology drugs with Japanese domestic sales of at least ¥5 billion in 2016

Company name	Drug name	2016 Sales (Billion, ¥)	Respiratory	Gastroenterology	Hematology	Breast	Urology	Head and neck	Other
Chugai Pharmaceutical Co., Ltd.	Bevacizumab	92.1	Yes	Yes	No	Yes	No	No	Yes
Chugai Pharmaceutical Co., Ltd.	Trastuzumab	34.1	No	Yes	No	Yes	No	No	No
Chugai Pharmaceutical Co., Ltd.	Rituximab	32.1	No	No	Yes	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Capecitabine	12.3	No	Yes	No	Yes	No	No	No
Chugai Pharmaceutical Co., Ltd.	Pertuzumab	11.9	No	No	No	Yes	No	No	No
Chugai Pharmaceutical Co., Ltd.	Alectinib	11.9	Yes	No	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Erlotinib	11.5	Yes	Yes	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Trastuzumab Emtansine	8.3	No	No	No	Yes	No	No	No
Ono Pharmaceutical Co., Ltd.	Nivolumab	103.9	Yes	No	No	No	No	No	Yes
Eli Lilly Japan K.K.	Pemetrexed	37.3	Yes	No	No	No	No	No	No
Eli Lilly Japan K.K.	Ramucirumab	28.9	Yes	Yes	No	No	No	No	No
Taiho Pharmaceutical Co., Ltd.	Tegafur/Gimeracil/Oteracil	26.9	Yes	Yes	No	Yes	No	Yes	No
Taiho Pharmaceutical Co., Ltd.	nab-Paclitaxe	20.7	Yes	Yes	No	Yes	No	No	No
Taiho Pharmaceutical Co., Ltd.	Calcium Folinate	9.7	No	Yes	No	No	No	No	No
Taiho Pharmaceutical Co., Ltd.	Tegafur, Uracil	6.5	Yes	Yes	No	Yes	Yes	Yes	Yes
Takeda Pharmaceutical Co., Ltd.	Panitumumab	18.8	No	Yes	No	No	No	No	No
Takeda Pharmaceutical Co., Ltd.	Leuprorelin	48.6	No	No	No	Yes	Yes	No	No
Novartis International AG	Imatinib	27.5	No	Yes	Yes	No	No	No	No
Novartis International AG	Nilotinib	20.7	No	No	Yes	No	No	No	No
Novartis International AG	Everolimus	15.1	Yes	Yes	No	Yes	Yes	No	No

Nippon Boehringer Ingelheim Co., Ltd.	Afatinib	8.7	Yes	No	No	No	No	No	No
Eisai Co., Ltd.	Eribulin	7.8	No	No	No	Yes	No	No	Yes
Yakult Honsha Co., Ltd.	Oxaliplatin	18.4	No	Yes	No	No	No	No	No
Daiichi Sankyo Co., Ltd.	Denosumab	13.9	Yes	Yes	Yes	Yes	Yes	Yes	Yes

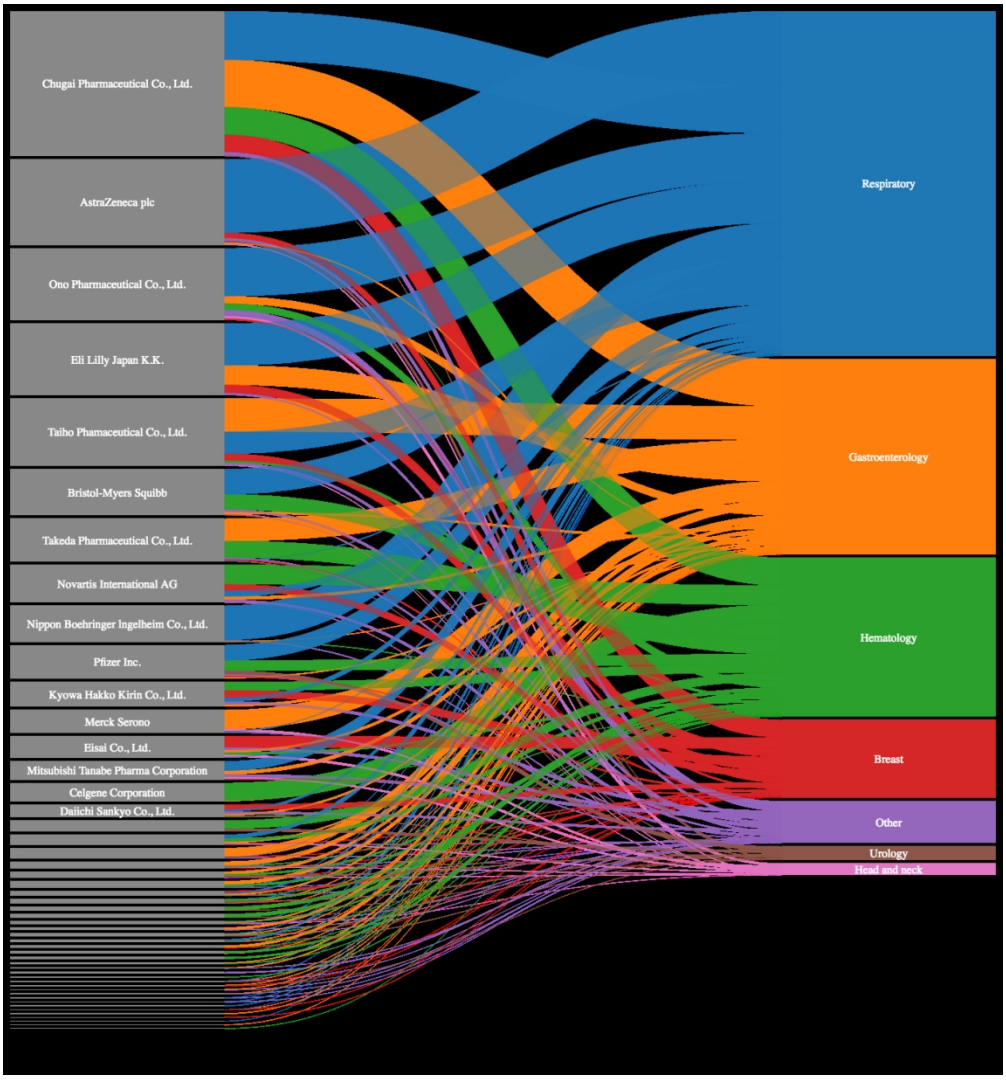

Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band colour represents the payment destination specialties. Due to space limitations, names of companies with payment values of less than ¥10 million [$8,885] have been omitted.

493x529mm (72 x 72 DPI)

Supplementary Material 1. 71 pharmaceutical companies sampled and the starting and ending date of the period when the payment data was disclosed

Pharmaceutical company	Period of the payment data in 2016	
	Starting date	Ending date
Maruho Co., Ltd.,	October 1, 2016	September 30, 2017
Shire Japan KK,	January 1, 2016	December 31, 2016
Fuso Pharmaceutical Industries, Ltd.,	April 1, 2016	March 31, 2017
POLA-Pharma.,	January 1, 2016	December 31, 2016
Nippon Zoki Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
Nippon Kayaku Co., Ltd.	April 1, 2016	March 31, 2017
Kowa Company. Ltd.,	April 1, 2016	March 31, 2017
Kracle Holdings, Ltd.,	January 1, 2016	December 31, 2016
Fujimoto Pharmaceutical Corporation,	July 1, 2016	June 30, 2017
Kyoto Pharmaceutical Industries, Ltd.	June 1, 2016	May 31, 2017
Merck Serono Co., Ltd.,	January 1, 2016	December 31, 2016
Nippon Chemiphar Co., Ltd.,	January 1, 2016	December 31, 2016
TOYAMA CHEMICAL CO., LTD.,	April 1, 2016	March 31, 2017
Bayer Yakuhin, Ltd.,	January 1, 2016	December 31, 2016
UCB Japan Co., Ltd.,	January 1, 2016	December 31, 2016
AYUMI Pharmaceutical Corporation,	April 1, 2016	March 31, 2017
CELGENE CORPORATION,	January 1, 2016	December 31, 2016
Senju Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Bristol-Myers Squibb K.K,	April 1, 2016	March 31, 2017
TOA EIYO LTD,	April 1, 2016	March 31, 2017
TSUMURA & CO.,	April 1, 2016	March 31, 2017
Toray Industries, Inc.,	April 1, 2016	March 31, 2017
TERUMO CORPORATION,	April 1, 2016	March 31, 2017
SEIKAGAKU CORPORATION,	April 1, 2016	March 31, 2017
Teikoku Seiyaku Co., Ltd.,	January 1, 2016	December 31, 2016

ASAHI KASEI PHARMA CORPORATION,	April 1, 2016	March 31, 2017
Wakamoto Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
MOCHIDA PHARMACEUTICAL CO., LTD.,	April 1, 2016	March 31, 2017
Santen Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
Mylan Seiyaku Ltd.,	January 1, 2016	December 31, 2016
Yakult Honsha Company, Limited.,	April 1, 2016	March 31, 2017
Minophagen Pharmaceutical Co.,	April 1, 2016	March 31, 2017
Taisho Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
ASKA Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Meiji Seika Pharma Co., Ltd.,	April 1, 2016	March 31, 2017
NIHON PHARMACEUTICAL CO., LTD.,	April 1, 2016	March 31, 2017
Maruishi Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
KYORIN Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
TEIJIN PHARMA LIMITED.,	April 1, 2016	March 31, 2017
ZERIA Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
SANWA KAGAKU KENKYUSHO CO., LTD.,	April 1, 2016	March 31, 2017
Kaken Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
Hisamitsu Pharmaceutical Co., Inc.,	March 1, 2016	February 28, 2017
Sanofi K.K.,	January 1, 2016	December 31, 2016
EA Pharma Co., Ltd.,	April 1, 2016	March 31, 2017
Nippon Boehringer Ingelheim Co., Ltd.,	January 1, 2016	December 31, 2016
Torii Pharmaceutical Co., Ltd.,	January 1, 2016	December 31, 2016
AstraZeneca plc	January 1, 2016	December 31, 2016
Sumitomo Dainippon Pharma Co., Ltd.,	April 1, 2016	March 31, 2017
Novartis Pharma K.K.,	January 1, 2016	December 31, 2016
Eli Lilly Japan K.K.,	January 1, 2016	December 31, 2016
ONO PHARMACEUTICAL CO., LTD.,	April 1, 2016	March 31, 2017
Kissei Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
Eisai Co., Ltd.,	January 1, 2016	December 31, 2016

NIPPON SHINYAKU CO., LTD.,	April 1, 2016	March 31, 2017
AbbVie GK,	January 1, 2016	December 31, 2016
Mitsubishi Tanabe Pharma Corporation,	April 1, 2016	March 31, 2017
Research Institute for Microbial Diseases,	April 1, 2016	March 31, 2017
MSD K.K.,	January 1, 2016	December 31, 2016
Janssen Pharmaceutical K.K.,	January 1, 2016	December 31, 2016
Kyowa Hakko Kirin Company, Limited,	January 1, 2016	December 31, 2016
Takeda Pharmaceutical Company Limited.,	April 1, 2016	March 31, 2017
TAIHO PHARMACEUTICAL CO., LTD.,	January 1, 2016	December 31, 2016
Otsuka Pharmaceutical Co., Ltd.,	January 1, 2016	December 31, 2016
DAIICHI SANKYO COMPANY, LIMITED.,	April 1, 2016	March 31, 2017
GlaxoSmithKline K.K.,	January 1, 2016	December 31, 2016
Shionogi & Co,. Ltd.,	April 1, 2016	March 31, 2017
Chugai Pharmaceutical Co., Ltd.,	January 1, 2016	December 31, 2016
Novo Nordisk Pharma Ltd.,	January 1, 2016	December 31, 2016
Astellas Pharma Inc.,	April 1, 2016	March 31, 2017
Pfizer Japan Inc.,	December 1, 2015	November 30, 2016

Supplementary Material 2. Monetary value of payment (¥) in each company according to oncology subspecialty

Company name	Respiratory	Gastroenterology	Hematology	Breast	Urology	Head and neck	Other	All
Chugai Pharmaceutical Co., Ltd.	25,061,169	24,264,112	14,242,968	8,958,305	229,104	0	1,787,018	74,542,676
AstraZeneca plc	37,680,325	662,651	55,685	2,770,885	890,960	456,618	1,319,735	43,836,859
Ono Pharmaceutical Co., Ltd.	24,623,912	3,718,073	3,396,785	890,961	0	1147112	3,129,497	36,906,340
Eli Lilly Japan K.K.	21,566,802	9,944,828	0	4,145,014	0	0	1,046,878	36,703,522
Taiho Pharmaceutical Co., Ltd.	11,248,370	17,134,599	1,202,796	3,530,431	0	222740	1,147,111	34,486,047
Bristol-Myers Squibb	13,019,156	1,058,015	7,735,684	33,411	278,426	300,699	1,314,166	23,739,557
Takeda Pharmaceutical Co., Ltd.	411,752	11,462,655	8,531,978	523,439	171,829	0	798,682	21,900,335
Novartis International AG	3,140,636	1,525,769	9,913,984	3,306,435	0	77,959	1,299,619	19,264,402
Nippon Boehringer Ingelheim Co., Ltd.	17,652,164	111,370	211,370	0	0	0	445,480	18,420,384
Pfizer Inc.	7,840,157	607,127	5,257,311	764,319	1,832,840	0	767,502	17,069,256
Kyowa Hakko Kirin Co., Ltd.	2,082,619	1,046,878	4,359,554	3,669,644	0	0	1,503,500	12,662,195
Merck Serono	467,754	9,722,368	0	33,411	0	946,645	412,069	11,582,247
Eisai Co., Ltd.	445,480	1,191,660	1,180,522	5,791,243	0	1135975	1,380,988	11,125,868
Mitsubishi Tanabe Pharma Corporation	4,844,593	1,780,235	44,548	389,795	0	813,002	1,458,947	9,331,120
Celgene Corporation	0	103,120	9,085,712	0	0	0	0	9,188,832
Daiichi Sankyo Co., Ltd.	1,124,842	915,086	222,740	2,615,204	389,796	0	1,084,466	6,352,134
Janssen Pharmaceutical K.K.	0	0	4,276,610	0	1,252,917	0	0	5,529,527
MSD K.K.	1,901,643	545,715	1,748,510	278,425	0	529,009	111,370	5,114,672
Yakult Honsha Co., Ltd.	288,740	4,248,928	0	381,548	0	0	175,306	5,094,522

Bayer AG	155,918	1,971,249	356,384	55,685	222,740	222,740	278,425	3,263,141
Sanofi K.K.	0	1,250,000	890,000	325,000	550,000	100000	50,000	3,165,000
Sumitomo Dainippon Pharma Co., Ltd.	278,425	1,626,004	1,124,837	0	0	0	77,959	3,107,225
Nippon Kayaku Co., Ltd.	774,021	679,357	55,685	800,124	22,274	0	122,507	2,453,968
Astellas Pharma Inc.	390,000	100,000	900,000	100,000	520,000	0	0	2,010,000
Asahi Kasei Pharma Corporation	0	114,552	1,659,413	0	111,370	0	0	1,885,335
Nippon Shinyaku Co., Ltd.	0	0	1,748,509	0	111,370	0	0	1,859,879
Otsuka Pharmaceutical Co., Ltd.	100,000	440,000	607,912	0	0	46286	200,000	1,394,198
Zeria Pharmaceutical Co., Ltd.	0	1,113,700	0	0	0	0	222,740	1,336,440
Shionogi & Co., Ltd.	360,920	329,984	309,360	103,120	0	0	134,056	1,237,440
Kyorin Pharmaceutical Co.,LTD.	845,584	72,184	72,184	0	206,241	0	0	1,196,193
Tsumura & Co.	0	1,080,290	55,685	55,685	0	0	0	1,191,660
Teijin Pharma Limited	170,000	70,000	850,000	0	0	0	0	1,090,000
Sanwa Kagaku Kenkyusho Co., Ltd.	0	0	890,960	0	0	0	0	890,960
AbbVie GK	0	467,754	245,014	0	0	0	0	712,768
Terumo Corporation	110,440	430,716	0	0	0	0	110,440	651,596
Kowa Company, Limited	0	0	0	0	0	0	556,851	556,851
Novo Nordisk Pharma Ltd.	0	0	360,925	0	0	0	0	360,925
Meiji Seika	154,680	51,560	0	51,560	0	0	72,184	329,984
Aska Pharmaceutical Co., Ltd.	0	111,370	0	77,959	111,370	0	0	300,699
Nippon Chemiphar Co., Ltd.	0	167,055	0	0	0	0	111,370	278,425

Kracie Pharmaceutical, Ltd.	0	61,872	0	0	0	0	206,240	268,112
Ayumi Pharmaceutical Corporation	154,680	0	0	0	0	0	72,184	226,864
Kissei Pharmaceutical Co., Ltd.	111,370	0	0	0	0	0	111,370	222,740
Teijin Home Healthcare Limited	190,000	0	0	0	0	0	0	190,000
Hisamitsu Pharmaceutical Co., Inc.	22,274	33,411	0	111,370	0	0	0	167,055
EA Pharma Co.,Ltd.	0	154,680	0	0	0	0	0	154,680
Torii Pharmaceutical Co., Ltd.	0	0	0	103,120	0	0	0	103,120
Mochida Pharmaceutical Co., Ltd.	0	55,685	0	0	0	0	0	55,685
Nihon Pharmaceutical Co., Ltd.	0	0	55,685	0	0	0	0	55,685
GlaxoSmithKline plc	55,685	0	0	0	0	0	0	55,685

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-9
Objectives	3	State specific objectives, including any prespecified hypotheses	8-9
Methods			
Study design	4	Present key elements of study design early in the paper	9-13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	11-12
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	12

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-14
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	14-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-22
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22-23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Pharmaceutical payments to certified oncology specialists in Japan in 2016: a retrospective observational cross-sectional analysis

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Abstract (299 words)

Objective: This study aimed to elucidate the characteristics of payments from pharmaceutical companies to oncology specialists in Japan, whether the payment was made for promotional purposes, and whether there are specific rules to cover Conflict of Interest (COI) matters among the oncology specialists.

Design, Setting, and Participants: The participants were oncology specialists certified by the Japanese Society of Medical Oncology (JSMO) up to 2016. We retrospectively extracted 2016 payment data reported by 78 Japanese pharmaceutical companies.

Outcome measures: We identified payments to the individual specialists, employed several regression approaches to estimate factors associated with higher value payments, made a Sankey diagram to illustrate the payment flow from the companies to oncology specialties, analyzed oncology drugs with annual sales of ¥5 billion [£33.9 million, €40.2 million, $46.0 million] or above (hereafter high-income drugs) and examined the JSMO policy for oncology specialists disclosing COIs.

Results: In total, 59 companies made at least one payment to the oncologists, and the total monetary value was ¥585,453,314 [£3,963,800, €4,702,436, $5,381,005]. Of the 1080 specialists sampled, 763 (70.6%) received at least one payment while 317 received no payment at all. Of the 763, a small group of 142 (13.1%) receiving at least ¥1 million [£6.8 thousand, €8.0 thousand, $9.2 thousand] accounted for 71.5% of the total (¥418,345,258 [£2,832,398, €3,360,203, $3,845,085]). After adjustment of covariates, working for university hospitals and for cancer hospitals were key factors associated

with larger monetary payments. Payments were likely to be made toward the specialties using high-income drugs, though the tendency differed between companies. The JSMO has its own COI policy for its members but it did not specifically mention its certified oncology specialists.

Conclusion: Substantial financial relationships were observed between pharmaceutical companies and oncology specialists, but their extents varied significantly between individuals. There should be specific COI rules covering oncologists.

Keywords: conflict of interest; oncology specialist; Japan; industry payment; Japanese Society of Medical Oncology

Article summary (Strengths and limitations of this study):

- ✓ We considered oncology specialists certified by the Japan Society of Medical Oncology, which is one of the largest professional medical associations in the clinical oncology field of Japan.

- ✓ The authors independently organized payment data for oratory, writing, and consulting work, as published by the major pharmaceutical companies, and created a single uniform payment database.
- ✓ Accuracy of the affiliations and subspecialties of some oncology specialist in the study year (2016) were estimated using the data on the affiliation websites and other data sources on the Internet, possibly causing some measurement errors in these variables.
- ✓ This study only covered limited types of payment data in the single year (2016), which hampered a comprehensive and/or longitudinal analysis of the type and value of the payment among the oncology specialists.

Word count: 4,255

Introduction

Cancer has been the leading cause of mortality in Japan since 1981. The government introduced its first Comprehensive 10-year Strategy for Cancer Control (1984-1993), followed by a New 10-year Strategy to Overcome Cancer (1994-2003) and a third

Comprehensive 10-year Strategy for Cancer Control in 2014, aimed at boosting cancer research and provide high-quality cancer interventions and services. In 2015, an "Acceleration Plan for Cancer Control" was proposed with three key foci, "prevention", "treatment/research" and "coexistence with cancer", with a Basic Plan to Promote Cancer Control Programs being approved in 2017. In 2016, the year our study covered, there were 372,986 cancer deaths in Japan, with malignant neoplasms costing the nation an estimated ¥3.6 trillion [£24.4 billion, €28.9 billion, $33.1 billion] in medical expenditure. In males, lung cancer was the leading cause of cancerous deaths (52,430) in 2016, followed by gastric cancer (29,854) and colorectal cancer (27,026), while colorectal cancer was the leading cause of cancerous death in females (23,073), followed by lung cancer (21,408) and colorectal cancer (17,405), in the same year.[1] The risk factors for cancer are diverse, including tobacco use, infection, obesity, radiation exposure, reproductive and hormonal factors, and other environmental and occupational pollutants and carcinogens.[2] In case of Japan, primarily with the population ageing, its cancer death is estimated to continuously increase in future.[1]

For the pharmaceutical industry, medical and therapeutic practice generates substantial income, allowing it to satisfy market demand and exploit various opportunities to

expand their own profits.[3-5] From the 1950s, the main business model of the pharmaceutical industry was the production of low-price drugs to treat diseases and conditions that were primarily chronic and prevalent (e.g. hypertension and diabetes).[6-8] Following advances of drug development against infectious and chronic diseases, cancer became an ever-increasing and major problem, with 17.2 million incidents and 213.2 million cancer-associated disability-adjusted life-years (DALY) lost during 1990-2016 worldwide.[9] The pharmaceutical industry therefore adopted a new business model, discovery and development of anticancer agents that could be sold at extremely high price, but usually for short treatment durations.[3-5] This guaranteed a hefty profit in a short timeframe - provided that the drugs would be prescribed and used - while imposing an extraordinarily high cost on patients and health systems.[3-5 10] Indeed, a single administration of tisagenlecleucel, a recently-approved chimeric antigen receptor T-cell immunotherapy manufactured by Novartis Pharma, reportedly costs $475,000.[11]

Physicians remain paramount decision-makers on the demand-side of the pharmaceutical market. Even subtle financial interactions between physicians and a pharmaceutical company are known to affect their prescribing behavior,[12-17] and could encourage irrational or preferential use of a company's drug. Unsurprisingly, given the

cost of anticancer drugs, oncologists have latterly become primary targets for approaches from companies with high-cost anticancer products to sell. Indeed, significant financial relationships between such companies and the authors of the Clinical Practice Guidelines (CPGs) issued by the National Comprehensive Cancer Networks (NCCN) in the United States have been reported.[18] Given these far from ideal circumstances, there has been a growing need for intervention, in the form of policy implementation and education about the implications of these interactions to help protect doctors, patients, institutions and the companies themselves.[14-17] Consequently, medical and governmental facilities worldwide are considering guidelines, self-regulation and legislative checks to help control the relationship between physicians and the pharmaceutical industry, exemplified by the USA's Physician Payments Sunshine Act, enacted in 2010.[19 20]

Although Japan has the world's third largest pharmaceutical market, with annual sales of $76 billion in 2017,[21] its overall scale has been declining at approximately 2% annually.[22] To maintain sales in these competitive and tightening markets, forceful advertisement of high-price products, namely novel oncology drugs, has become increasingly important for pharmaceutical companies. Indeed, sales of oncology drugs

have recently been rising in Japan, exceeding ¥1 trillion [£6.8 billion, €8.0 billion, $9.2 billion] for the first time in 2016.[23] Furthermore, sales are predicted to increase 1.5–fold in the next decade with the increasing application of immunotherapy in clinical practice.[23] It would be reasonable to assume that pharmaceutical companies will increasingly deploy marketing measures and incentives targeting oncology specialists for the immediate and foreseeable future.

In Japan, the Japan Pharmaceutical Manufacturers Association (JPMA) covers a majority of companies that manufacture brand name drugs in Japan. Its members accounted for 80.8% of total pharmaceutical sales in Japan in 2015.[24] In 2011, the JPMA published transparency guidelines requiring all member companies to disclose all payments for speaking, writing and consulting made to all individuals, specifying their names and affiliations.[25] The aim was to improve the transparency of linkages between pharmaceutical companies and physicians, as in the Open Payments Database in the United States.[19 20] However, the disclosure format, whereby companies involved published the required data on their own individual websites, has differed among and between companies and the aggregated, standardized payment data have not been

readily available.[26] As a result, an examination of company/physicians links and payments in a meaningful way has proved almost impossible.

The aims of the current study were: 1) to understand and evaluate the characteristics and distributions of financial payments made by pharmaceutical companies to oncology specialists: 2) to examine a well-accepted belief that pharmaceutical companies make payments to promote their products; and 3) to elucidate what Japanese oncology specialists are obliged to disclose with respect to any conflicts of interest.

Methods

Study setting and participants

The Japan Society of Medical Oncology (JSMO), with over 9154 general members, is the one of the largest professional medical societies in the clinical oncology field in Japan. The JSMO began operating a specialty registration system for members in 2004. This required JSMO members wishing to be certified to meet specific requirements for both oncology care and academic achievement. Only after passing the requisite examination, could they become board-certified oncology specialists with renewed

certification of every 5 years. We included all oncology specialists certified by the JSMO as of April 1st, 2016.

Sources of Payment Data

The sources of the payment data were the websites of the 78 pharmaceutical companies involved in this study. These companies publish data of payments made to physicians and other researchers annually under the transparency guidelines of the JPMA. They were categorized into 71 active JPMA members, six affiliated entities of these companies, and one past member. The companies included in this study, plus the starting and ending dates of their payment data, are listed in Supplementary Material 1.

We obtained each company's data and organized them into a unified single database. This was done because no data was published as a spreadsheet, so data with character codes were converted into a spreadsheet format and data with no character codes were converted into text files using an Optical Character Reader. Moreover, where data was protected against facsimile or reproduction, we used FullShot10 software (Inbit, CA, USA) to scan photos of the data and converted the data into text files. The accuracy of the re-organized data was confirmed by comparing it with the original data. The

database included physicians' names, their main institutional affiliation, payments received, the form of the payments, and the total amount paid. The form of payment was categorized into three types; payment for speaking engagements, payment for writing or publication work, and consulting fees. For the purposes of this study, we converted Japanese yen (¥) to Pound Sterling (£), Euro (€), and US dollars ($), using the average monthly exchange rate for 2016, namely ¥147.7 per £1, ¥124.5 per €1 and ¥108.8 per US$1.

Data collection

We examined payment data for all oncology specialists included in this study. We extracted their working institutions and regional locations, along with the year of their certification by the JSMO. We further confirmed the accuracy of such information in the year 2016, collating data from institutional websites and other sources. We speculated the cancer specialties (respirology, gastroenterology, hematology, breast, etc.) of all oncologists who received total payment of ¥1 million [£6.8 thousand, €8.0 thousand, $9.2 thousand] or above from the included pharmaceutical companies, using data from institutional websites and other sources as well. In general, ¥1 million is approximately 25% of the median annual income of a Japanese citizen.[27] In addition, we

sought to examine any prevailing COI policy from the JSMO website that could apply to oncologists.

Data analysis

To examine the characteristics and distributions of payments, we performed descriptive analyses of the data on an individual oncology specialist and pharmaceutical company basis. We then summarized the characteristics of oncology specialists according to the total monetary value of the payment they received, dividing the patients into the three groups; ¥1 million or above (High-payment Group); ¥1 – 1 million (Low-payment Group), and ¥0 (No-payment Group).

Using a multivariate negative binomial regression model, we subsequently examined possible factors associated with the monetary value of the payment to the individual oncologists, using institutional place of work, regional working locations, and year of experience after board certification as covariates. The payment data was rounded off as a unit of ¥1 million. Further, to assess the effects of the cancer specialty on the value of the payment, using a zero-truncated negative binomial model, we repeated the analysis in High-payment Group. In addition, for Low-payment and No-payment Groups we

examined possible factors associated with the monetary value of the payment to the individual oncologists, using the same model adopted as for the overall population. For this analysis, the payment data was rounded off as a unit of ¥100,000 [£677, €803, $919]. Second, we created a Sankey diagram among the specialists in this cohort to illustrate the distribution of the payment to each specialty on an individual company basis. The Sankey diagram is a flow diagram, where band width proportionally represents the flow quantity.[28] Payment values from individual companies, according to cancer specialty, are depicted in the bands in the diagram, width being proportional to the total amount of the payment. In addition, to see whether the payment was linked to any specific oncology drugs, we examined such drugs with annual Japanese domestic sales of ¥5 billion [£33.9 million, €40.2 million, $46.0 million] or above in the fiscal year of 2016, and if each drug was covered under the Japanese National Health Insurance scheme in specific oncology subspecialty by the end of the same year (March 31, 2017). We further examined newly-approved drugs and drugs with an added indication during the fiscal years of 2015 and 2016 (April 1, 2015 to March 31, 2017).

Human subject involvement

The present study is a retrospective analysis of existing databases and public domain information. No patients or any other individuals were other than unnamed oncology specialists were included in the study.

Results

The JSMO had over 9000 members at the time the study was undertaken, with 1081 physicians having been board certified as oncology specialists. We excluded one oncologist whose professional affiliation we were unable to confirm, and he did not receive any payment from the pharmaceutical companies. Thus, we included a total of 1,080 specialist oncologists in our analyses.

Table 1 summarizes the details of certified oncologists and payments from Japanese pharmaceutical firms. Of the 1080 selected certified oncology specialists, 442 (40.9%), 183 (16.9%), and 455 (42.1%) worked for university hospitals, cancer hospitals, and other institutions, respectively. The number of specialists certified by the JSMO from 2004 onwards was largest in 2013 (143 [13.2%]), the number of new certifications displaying a downward trend during the subsequent years (2014 [98, 9.1%], 2015 [85, 7.9%], and 2016 [76, 7.0%]).

A total of 7325 payments were recorded, the total monetary value being ¥585,453,314 [£3,963,800, €4,702,436, $5,381,005]. Of this total, ¥467,802,690 [£3,167,249, €3,757,451, $4,299,657] was for speaking engagements, ¥94,682,807 [£641,048, €760,504, $870,246] was for consulting services, and ¥22,266,186 [£150,753, €178,845, $204,652] was paid for writing work. The median monetary value and count of an individual payment was ¥120,016 [£813, €964, $1,103]. (interquartile range (IQR) ¥ 0 – ¥449,378 [£3,043, € 3,609, $4,130] and 2 (IQR 0–7), respectively.

Of the 1080 individuals, 763 (70.6%) received at least one payment. Furthermore, 142 (13.1%) received payments totaling ≥¥1 million, while 19 (1.8%) received ≥¥5 million [£33.9 thousand, €40.2 thousand, $46.0 thousand]. Two individuals (0.2%) received ≥¥10 million [£67.7 thousand, €80.3 thousand, $91.9 thousand].

Table 2 summarizes the monetary values and counts of payments made by the 78 pharmaceutical companies. In total, 59 (75.6%) companies made at least one payment to oncology specialists. The Chugai Pharmaceutical Co. Ltd., a subsidiary of F. Hoffmann-La Roche Ltd, made the largest accumulated payment of ¥103,830,493 [£702,982, €

833,980, $954,324]. The median monetary value and count among the 78 companies was ¥645,947 [£4,373, €5,188, $5,937] (IQR ¥33,410 [£226, €268, $307] – ¥5,196,201 [£35,181, €41,737, $47,759] and 10 (IQR 1 – 71), respectively.

Table 3 ranks the oncology specialists according to the monetary value of the payments they received. In High-payment Group, 52.8% (75) of the oncologists worked for university hospitals, while 28.2% (40) worked for cancer hospitals: these figures were larger than those seen in the other two groups. Further, while only 19.7% (28) of the specialists in High-payment Group were certified during the previous five years (2012 to 2016), 49.4% (307) and 60.3% (191) of Low-payment and No-payment Groups respectively were certified during these five years. The top three cancer specialties attracting payments were respirology (53 [37.3%]), gastroenterology (32 [22.5%]), and hematology (29 [20.4%]).

In Group A, the total monetary value paid and number of payments were ¥418,345,258 [£2,832,398, €3,360,203, $3,845,085] and 4466, respectively, accounting for 71.5% and 61.0% of the totals, with the largest three specialties of respirology (¥166,220,775 [£1,125,395, €1,335,107, $1,527,764], 39.7%), gastroenterology (¥91,319,282

[£618,275.00, €733,488, $839,332], 21.8%) and hematology (¥84,186,048 [£569,980, €676,193, $773,769], 20.1%).

Table 4 displays findings of the multivariate regression analyses for the monetary value of payments. Oncologists with longer experience after board certification were significantly more likely to receive larger payments compared with those with shorter experience after certification (relative monetary value (RMV)=1.32, 95% CI=1.26 – 1.39). Those working for university hospitals (RMV=2.98, 95% CI=2.11 – 4.21) and those working for cancer hospitals (RMV=3.19, 95% CI=2.14 – 4.76) also tended to receive higher payments compared with those working for other types of institutions. The trends observed in Group A were not reflected in Groups B and C: in these groups, there were no significant differences in the monetary value of the payment depending on the type of affiliation. Those working in respirology were likely to receive higher payments compared with all others, although this trend was not statistically significant.

Figure 1 displays payment distributions to each cancer specialty on an individual company basis. Details of the payments are provided in Supplementary Material 2. Further, in Supplementary Material 3, we summarize the list of oncology drugs with

Japanese domestic sales of ¥5 billion or more. Chugai Pharmaceutical Co., Ltd. made the largest specialty payment of ¥74,376,669 [£503,566, €597,403, $683,609] and the top four specialties were respirology (¥24,545,685 [£166,186, €197,154, $225,604], 33.0%), gastroenterology (¥23,656,984 [£160,169, €190,016. $217,436], 31.8%), hematology (¥14,432,072 [£97,712, €115,920, $132,648], 19.4%), and breast cancer (¥8,958,305 [£60,652, €71,954, $82,337], 12.0%). The Chugai company manufactured eight oncology drugs with annual sales of ¥5 billion or more (Supplementary Material 3), and three, three, one, and five drugs were respectively covered under the National Health Insurance scheme for the field of respirology, gastroenterology, hematology and breast. Nivolumab, manufactured by the Ono Pharmaceutical Co., Ltd., mainly used in lung cancer and melanoma, had the largest domestic sales in 2016 (¥103.9 billion [£703.5 million, €834.5 million, $955.0 million]). The total monetary value of the company's payments was ¥35,035,323 [£237,206, € 281,408, $322,016], (representing fourth place in the payment table), of which ¥22,619,251 [£153,143, €181,681, $207,898], (64.6%) was specifically distributed for respirology work. All of the top eight companies with regard to the monetary value of the payments (Supplementary Material 2) had at least one drug which was newly approved that with an added indication under the National Health Insurance scheme in the fiscal years of 2015 and

2016. While AstraZeneca plc had no oncology drugs with Japanese domestic sales of at least ¥5 billion (Supplementary Material 3), vandetanib and osimertinib was newly approved for thyroid cancer in September 28, 2015 and non-small cell lung cancer in March 28, 2016, respectively (Supplementary Material 4). The total monetary value of the company's payments was second, accounting for ¥42,544,963 [£288,050, €341,727, $391,038]. Of the total, 86.0% (¥36,577,758 [£247,649, €293,797, $336,193]) was specifically distributed for respirology work.

The JSMO has guideline on the COI disclosure for its members. Its members are required to disclose their COIs associated with publications and other research presentations. Further, executive board members, auditors, and other high-class members, as well as presidents and vice-presidents of conferences and committee members under the JSMO are required to disclose their COIs associated with their works and positions. These include, with respect to any for-profit organization, reporting any 1) Position as an officer or advisor, 2) Stock ownership, 3) Patent royalties or licensing fees, 4) Honoraria (e.g. lecture fees), 5) Fees paid for any writing or publication work, 6) Receipt of research funding, 7) Advisory fees or financial remuneration in exchange for testimony, 8) Acceptance of researchers from any for-

profit enterprise, 9) Endowed chairs offered, and 10) Remuneration (travel, gifts, or other in-kind payments not directly related to research). However, there are no specific rules specifically referring to oncology specialists.

Discussion

In 2016, approximately ¥600 million [£4.1 million, €4.8 million, $5.5 million] was paid by Japanese pharmaceutical companies to 763 (70.6%) certified oncology specialists. Payments appeared to be concentrated on specific targets, notably experienced oncologists working for university hospitals and cancer hospitals.

The proportion of oncologists receiving payments was larger compared with general physicians in the US (48.0%)[29] and Japan (33.3%).[30] However, the proportion was slightly smaller than that of NCCN oncology CPG authors in the US (86.4%).[18] Although the mean value of payments in our study was approximately half of that of the CPG authors ($4,888 [data not shown] vs.$10,011), a simple comparison is not valid, as our analysis did not include payments related to meals, transportation and accommodation, stock ownership, investment interest, or payments from medical device companies.[29] The CPG authors strongly influence oncology practice, both in the US and

internationally,[31] by recommending treatment algorithms. They thus become prime targets for pharmaceutical companies selling anticancer products. It is reasonable to assume that Japanese pharmaceutical companies with similar anticancer interests would target oncology specialists in an attempt to boost the sales and use of their specific products.

We observed a large disparity in payments to specialists. Those receiving ¥1 million or more accounted for 13.1% of all oncologists studied but received 71.5% of the total paid. Oncologists working for university hospitals and those working for cancer hospitals similarly received large value payments. In Japan, cancer centers are generally more likely to treat more cancer patients compared to university hospitals. Indeed, cancer centers top the nationwide ratings for treatments of most of the common cancers, including lung, colon, gastric, and breast cancer.[32] In contrast, university hospitals are regarded as symbols of academic excellence and authority, and medical school professors traditionally have a strong influence on both physicians and medical practice in their field of expertise. They are more influential in setting treatment protocols which are usually followed without question by less senior medical staff nationwide. Thus, our findings suggest that Japanese pharmaceutical companies have placed emphasis on

expertise and authority, as well as clinical experience, in the selection of targets for their promotional activities.

We found that respirology attracted the greatest financial outlay. In Japan, lung cancer is of primary concern at present, covering a large patient volume and consequently attracting multiple novel oncology drugs, such as alectinib (Chugai Pharmaceutical Co., Ltd., [2014]), nivolumab (Ono Pharmaceutical Co., Ltd, [approved 2015]), afatinib (Nippon Boehringer lngelheim Co., Ltd., [2016]), certinib (Novartis Pharma K.K., [2016]), osimertinib (AstraZeneca plc, [2016]), pembrolizumab (MSD K.K., [2016]), ramcirumab (Eli Lilly Japan K.K., [2016]), all for non-small cell lung cancer (Supplementary Materials 3 & 4). As such, for the pharmaceutical companies, this field is a critical yet highly competitive target in any strategy to maximize the cost-effectiveness of their promotional endeavors.

The examples of Chugai Pharmaceutical and Ono Pharmaceutical chiefly support the belief that there is an association between the value and destination of payments dependent on the products the companies in question manufacture. In contrast, the example of AstraZeneka confirms the idea that that funds were mainly allocated to

promote their novel product: osimertinib was approved for non-small cell lung cancer in March 2016. Indeed, 86% of the company's payment was allocated to respirology.

As we have demonstrated, there is an emphatic financial relationship between pharmaceutical companies and oncologists. It is true that the receipt of the abovementioned payments in Japan is not illegal, as they are supposedly given as remuneration for work undertaken or services rendered. However, we believe that there is an ethical problem inherent in such relationships, given that this practice could have been instigated and developed to possibly end up expanding the profit of pharmaceutical companies, rather than promoting the health and well-being of patients. Indeed, even a subtle but reputable financial relationship with the industry, such as collaborating in a field trial, could bias a physician's prescription patterns in a manner that benefits the companies.[12-17] Oncologists in Japan handle extraordinary and very potent life-saving drugs, and have a degree of autonomy in their prescribing actions. Their decisions substantially influence the treatment and outcome for their patients, as well as having significant economic impact due to the high cost of anticancer medications.[3-5] It would therefore appear sensible to have rigorous regulations in place which necessitate the open and accessible reporting of any financial dealings between

physicians and pharmaceutical companies, so as to avoid any potential nefarious or underhand behavior or undue pressure on physicians to alter their usual treatment practices. Indeed, it is possible that these highly-questionable arrangements may have contributed to the multiple cases of scientific misconduct that have recently been reported in Japan. The most infamous case was when employee misconduct was discovered in a series of clinical trials for Valsartan, an antihypertensive medication manufactured by Novartis Pharma, leading to a retraction of the associated academic papers.[33 34] A breast cancer clinical trial (CREATE-X trial) with a questionable pharmaceutical payment has also been identified.[35 36]

To prevent similar cases in future, we call for the implementation of a transparent, independent mechanism that would enable a comprehensive assessment of any and all payments being made by any pharmaceutical company to any individual physician or, for that matter, medical institution where the company's products may be used - and not just with respect to oncology. This has to be mandatory and legally-binding on the side of both the company and physician. New schemes along these lines, such as the US's Open Payments Database, may prove successful but it is too soon to know.[37] The Disclosure UK mechanism may not prove to be so effective as it is voluntary.

Additionally, given that such mechanisms allow for direct comparison between what is allegedly paid and what is allegedly received, it will necessitate a fair, equitable and timely mechanism for dispute settlement, probably involving the use of third parties.[36]

Concluding remarks

Japanese certified oncologists receive financial payments directly from pharmaceutical companies, usually from those active in the specialist field of the physician in question. This raises several queries with regard to ethical, medical, corruption and possibly legal issues. The value and specialty targets of the payments varied substantially, which also raises yet more questions as to why. We believe that the lessons learned from our analyses should be shared among the global medical community to help put in place safeguards to prevent undue and unethical inducements from the pharmaceutical industry and to help protect physicians from outside influences. It is essential to establish a robust, comprehensive and legally-binding system for identifying and avoiding any and all potential conflicts of interest, of any nature, involving physicians or other medical professionals, both in Japan and internationally. While it is too early to evaluate whether similar systems, such as the US-based Open Payments Database, will be truly effective, financial transparency is a fundamental component in illustrating that

there is an open, honest and ethically correct relationship between pharmaceutical companies and physicians. A more comprehensive study is planned, to include all Japanese oncologists, to try and confirm our findings and to help identify the best way forward to ensure that COI are avoided and so that physicians and pharmaceutical companies can work harmoniously and synergistically to provide Japan with the best cancer prophylaxis, treatment and cure possible.

Study Limitations

Several limitations in this preliminary study should be acknowledged. First, there could be measurement errors in the affiliations and subspecialties of the included speculates, as we speculated the accuracy of these data in the study year (2016), mainly using the affiliation websites and other data sources on the Internet. Second, there might be minor measurement errors in the payment database as well. Most of the pharmaceutical companies involved did not disclose their payment data in a uniform or readily available format. As a result, we manually entered all the payment data from a variety of formats, and, despite repeated and careful review, the database may include minor errors. Third, the present research analyzed only limited payment types. Currently, Japanese pharmaceutical companies do not disclose payment data for stock interest, loyalties, and

costs of meals, transportation, and accommodation. As, unlike the pharmaceutical companies, the JMSO and other similar academic and learned societies in Japan, where such data may be registered, refuse to open their databases to public scrutiny, we were not able to consider these data in this study. Fourth, most of the pharmaceutical companies only publish single year data so we could only consider payments made in 2016. To understand temporal trends and the extent and distribution of pharmaceutical company payments, a continuous assessment of the payment data is warranted in future.

Ethics approval

This study was approved by the Institutional Review Board of the Medical Governance Research Institute (MEGRI) on 16th May 2018.

Author contributors

AO acquired and controlled all sources of data, and oversaw all data analyses.

AO, HS, YO, TS, YShim, YSom, AT, and TT were involved in the study concept and design.

AO, HS, YO, TS, YShim, YSom, AT, and TT were involved in the analysis, interpretation of results and formation of conclusions.

A.O. drafted the manuscript.

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Role of funding source

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Conflict of Interest statement

AO and TT receive personal fees from Medical Network Systems (MNES Inc.); HS has received an honorarium from TAIHO Pharmaceutical Co., Ltd. for research outside the purview of work carried out during this study. All other authors declare no conflict of interests.

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Data availability statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Figure legends

Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band color represents the payment destination specialties. Due to space limitations, names of companies with payment values of less than ¥10 million (£67.7 thousand, €80.3 thousand, $91.9 thousand) have been omitted.

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Table 1. Characteristics of oncology specialists and pharmaceutical payment received by individual doctors.

Variable	
1. Characteristics of oncology specialists (N=1080)	
Working institutions (N, %)	
University hospitals	442 (40.9)
Cancer hospitals	183 (16.9)
Other types of institutions	455 (42.1)
Working regions (N, %)	
Hokkaido	52 (4.8)
Tohoku	58 (5.4)
Kanto	302 (28.0)
Chubu	194 (18.0)
Kinki	208 (19.3)
Chugoku	88 (8.2)
Shikoku	43 (4.0)
Kyushu	135 (12.5)
Year of certification (N, %)	
2006	45 (4.2)
2007	77 (7.1)
2008	71 (6.6)
2009	98 (9.1)
2010	133 (12.3)
2011	130 (12.0)
2012	124 (11.5)
2013	143 (13.2)
2014	98 (9.1)
2015	85 (7.9)
2016	76 (7.0)
2. Characteristics of payment (N=1080)	
Total payment	
Variable	585,453,314 [3,963,800]
Total count of payment	7,325
Type of payment (¥ [£], %)	
Speaking	467,802,690 [3,167,249], 79.9
Consulting	94,682,807 [641,048], 16.2
Writing	22,266,186 [150,753], 3.8
Missing	701,631 [4,750], 0.1
Payment per individual specialist	
Median value per individual specialist (¥ [£], Interquartile range)	120,016 [813] (0 [0] – 449,378 [3,043])
Median count per individual specialist (Interquartile rage)	2 (0–7)
Number of oncology specialists with payment (N, %)	
Any	763 (70.6)
¥1 million [£6.8 thousand] or above	142 (13.1)

¥5 million [£33.9 thousand] or above	19 (1.8)
¥10 million [£67.7 thousand] or above	2 (0.2)

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

Table 2. Companies making a payment to oncology specialists and monetary value and count of their payment

Pharmaceutical company	Monetary value (¥ [£])	Count
Chugai Pharmaceutical Co., Ltd.	103,830,493 [702,982]	1,248
AstraZeneca plc	51,928,785 [351,583]	592
Taiho Pharmaceutical Co., Ltd.	50,723,560 [343,423]	688
Ono Pharmaceutical Co., Ltd.	47,831,737 [323,844]	624
Eli Lilly Japan K.K.	44,825,340 [303,489]	502
Bristol-Myers Squibb K.K.	33,443,966 [226,432]	405
Takeda Pharmaceutical Company Ltd.	28,280,960 [191,476]	306
Novartis Pharma K.K.	27,203,346 [184,180]	336
Nippon Boehringer Ingelheim Co., Ltd.	25,987,859 [175,950]	325
Kyowa Hakko Kirin Company, Ltd.	20,208,095 [136,819]	267
Pfizer Japan Inc.	16,509,478 [111,777]	185
Merck Serono Co., Ltd.	16,377,746 [110,885]	229
Eisai Co., Ltd.	16,309,136 [110,421]	220
Celgene Corporation	15,207,296 [102,961]	212
Daiichi Sankyo Company, Limited.	8,772,101 [59,391]	117
Bayer Yakuhin, Ltd.	8,340,481 [56,469]	97
Yakult Honsha Company, Limited.	8,318,026 [56,317]	121
Janssen Pharmaceutical K.K.	7,723,516 [52,292]	84
MSD K.K.	6,317,468 [42,772]	71
Sumitomo Dainippon Pharma Co., Ltd.	5,196,201 [35,181]	92
Nippon Kayaku Co., Ltd.	3,868,780 [26,194]	46
Astellas Pharma Inc.	3,590,000 [24,306]	53
Nippon Shinyaku Co., Ltd.	3,129,497 [21,188]	53
Asahi Kasei Pharma Corporation	3,102,452 [21,005]	45
Sanofi K.K.	2,592,500 [17,552]	31
Otsuka Holdings Co., Ltd.	2,204,198 [14,923]	40
Mochida Pharmaceutical Co., Ltd.	2,149,441 [14,553]	31
Teijin Pharma Limited.	2,099,790 [14,217]	27

AbbVie GK,	2,082,626 [14,100]	17
Shionogi & Co., Ltd.	1,948,968 [13,195]	28
Kyorin Pharmaceutical Co., Ltd.	1,918,033 [12,986]	34
Tsumura & Co.	1,681,688 [11,386]	21
Meiji Seika Pharma Co., Ltd.	1,289,000 [8,727]	24
Terumo Corporation	1,214,840 [8,225]	16
Kissei Pharmaceutical Co., Ltd.	1,124,840 [7,616]	9
Zeria Pharmaceutical Co., Ltd.	946,645 [6,409]	12
Mitsubishi Tanabe Pharma Corporation	935,508 [6,334]	17
EA Pharma Co., Ltd.	783,712 [5,306]	17
Taisho Toyama Pharmaceutical Co., Ltd.	701,631 [4,750]	11
Kowa Company, Ltd.	590,262 [3,996]	5
Hisamitsu Pharmaceutical Co., Inc.	539,030 [3,649]	11
Novo Nordisk Pharma Ltd.	474,360 [3,212]	8
Sanwa Kagaku Kenkyusho Co., Ltd.	445,480 [3,016]	4
Aska Pharmaceutical Co., Ltd.	423,206 [2,865]	6
Shire Japan K.K	367,521 [2,488]	5
Nihon Pharmaceutical Co., Ltd.	311,836 [2,111]	8
Nippon Chemiphar Co., Ltd.	278,425 [1,885]	3
Ayumi Pharmaceutical Corporation	226,864 [1,536]	3
Mylan Seiyaku Ltd.	206,240 [1,396]	4
Kracie Holdings, Ltd.	134,056 [908]	2
GlaxoSmithKline K.K.	111,370 [754]	2
Minophagen Pharmaceutical Co.	110,440 [748]	2
Maruho Co., Ltd.	103,120 [698]	1
Torii Pharmaceutical Co., Ltd.	102,260 [692]	2
EN Otsuka Pharmaceutical Co., Ltd.	89,096 [603]	2
Kaken Pharmaceutical Co., Ltd.	77,959 [528]	1
Toray Industries, Inc.	77,080 [522]	1
Santen Pharmaceutical Co., Ltd.	51,560 [349]	1
Toyama Chemical Co., Ltd.	33,410 [226]	1
Bee Brand Medico Dental. Co., Ltd.	0 [0]	0

Biofermin Seiyaku Co., Ltd.	0 [0]	0
Fujimoto Pharmaceutical Corporation	0 [0]	0
Fuso Pharmaceutical Industries, Ltd.	0 [0]	0
Japan Tobacco Inc.	0 [0]	0
Kyoto Pharmaceutical Industries, Ltd.	0 [0]	0
Maruishi Pharmaceutical Co., Ltd.	0 [0]	0
Nippon Zoki Pharmaceutical Co., Ltd.	0 [0]	0
Otsuka Pharmaceutical Co., Ltd.	0 [0]	0
Otsuka Pharmaceutical Factory, Inc.	0 [0]	0
POLA-Pharma.	0 [0]	0
Research Institute for Microbial Diseases	0 [0]	0
Seikagaku Corporation	0 [0]	0
Senju Pharmaceutical Co., Ltd.	0 [0]	0
Taisho Pharmaceutical Co., Ltd.	0 [0]	0
Teikoku Seiyaku Co., Ltd.	0 [0]	0
Toa Eiyo Ltd.	0 [0]	0
UCB Japan Co., Ltd.	0 [0]	0
Wakamoto Pharmaceutical Co., Ltd.	0 [0]	0

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

Table 3. Characteristics of oncology specialists and pharmaceutical company payments received in 2016, according to the monetary value of the payment

Variable	High-payment Group (¥1 million [£6.8 thousand] or more) (N=142)	Low-payment Group (¥1 – 1 million [£6.8 thousand]) (N=621)	No-payment Group (¥0) (N=317)
I. Characteristics of oncology specialists			
Working institutions (N, %)			
University hospitals	75 (52.8)	248 (39.9)	119 (37.5)
Cancer hospitals	40 (28.2)	98 (15.8)	45 (14.2)
Other types of institutions	27 (19.0)	275 (44.3)	153 (48.3)
Working regions (N, %)			
Hokkaido	4 (2.8)	37 (6.0)	11 (3.5)
Tohoku	11 (7.8)	30 (4.8)	17 (5.4)
Kanto	45 (31.7)	162 (26.1)	95 (30.0)
Chubu	23 (16.2)	113 (18.2)	58 (18.3)
Kinki	29 (20.4)	108 (17.4)	71 (22.4)
Chugoku	9 (6.3)	60 (9.7)	19 (6.0)
Shikoku	5 (3.5)	31 (5.0)	7 (2.2)
Kyushu	16 (11.3)	80 (12.9)	39 (12.3)
Year of certification (N, %)			
2006	22 (15.5)	21 (3.4)	2 (0.6)
2007	15 (10.6)	46 (7.4)	16 (5.1)

2008	19 (13.4)	38 (6.1)	14 (4.4)
2009	19 (13.4)	56 (9.0)	23 (7.3)
2010	23 (16.2)	80 (12.9)	30 (9.5)
2011	16 (11.3)	73 (11.8)	41 (12.9)
2012	9 (6.3)	72 (11.6)	43 (13.6)
2013	9 (6.3)	79 (12.7)	55 (17.4)
2014	5 (3.5)	65 (10.5)	28 (8.8)
2015	2 (1.4)	51 (8.2)	32 (10.1)
2016	3 (2.1)	40 (6.4)	33 (10.4)
Subspecialty of oncologists (N, %)			
Respirology	53 (37.3)		
Gastroenterology	32 (22.5)		
Hematology	29 (20.4)		
Breast	16 (11.3)		
Head and neck	3 (2.1)		
Urology	1 (0.7)		
Other	8 (5.6)		
Characteristics of pharmaceutical payment			
Total payment			
Total value of payment (¥ [£])	418,345,258 [2,832,398]	167,108,056 [1,131,402]	
Total count of payment	4,466	2,859	
Type of payment (¥ [£], %)			
Speaking	327,075,925 [2,214,461], 78.2	140,726,765 [952,788], 84.2	
Consulting	73,870,218 [500,137], 17.7	20,812,589 [140,911], 12.5	
Writing	17,053,868 [115,463], 4.1	5,212,318 [35,290], 3.1	

Missing	345,247 [2,337], 0.1	356,384 [2,413], 0.2
Payment per individual specialist		
Median monetary value (¥ [£], Interquartile range)	2,269,622 [15,366] (1,439,448 [9,746] – 3,681,775 [24,927])	171,086 [1,158] (89,096 [603] – 380,886 [2,579])
Median count (Interquartile range)	24 [19 – 38]	3 (2 – 6)
Monetary value of payment according to subspecialties (¥ [£], %)		
Respirology	166,220,775 [1,125,395], 39.7	
Gastroenterology	91,319,282 [618,275], 21.8	
Hematology	84,186,048 [569,980], 20.1	
Breast	42,090,455 [284,973], 10.1	
Head and neck	8,689,962 [58,835], 2.1	
Urology	5,527,458 [37,424], 1.3	
Other	20,311,278 [137,517], 4.9	

684 We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

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Table 4. Multivariate regression models for the monetary value of payment on an individual basis

Variable	All (N=1080) Relative monetary value (95% CI)	Group A (N=142) Relative monetary value (95% CI)	Groups B and C (N=938) Relative monetary value (95% CI)
Year of experience after the board certification	1.32 (1.26 – 1.39)***	1.09 (1.02 – 1.17)**	1.12 (1.08 – 1.15)***
Types of affiliations			
Other type of institutions	Ref.	Ref.	Ref.
University hospitals	2.98 (2.11 – 4.21)***	2.14 (1.35 – 3.40)**	1.12 (0.93 – 1.35)
Cancer hospitals	3.19 (2.14 – 4.76)***	1.67 (1.00 – 2.78)*	1.14 (0.88 – 1.48)
Working region			
Kanto	Ref.	Ref.	Ref.
Hokkaido	0.58 (0.25 – 1.35)	0.83 (0.41 – 1.67)	1.06 (0.76 – 1.48)
Tohoku	1.55 (0.84 – 2.84)	1.35 (0.78 – 2.34)	1.14 (0.78 –1.68)
Chubu	0.90 (0.58 – 1.42)	0.85 (0.53 – 1.36)	1.12 (0.86 – 1.46)
Kinki	1.10 (0.72 – 1.68)	1.06 (0.67 – 1.68)	0.85 (0.64 – 1.13)
Chugoku	1.16 (0.52 – 2.60)	1.32 (0.58 – 2.97)	0.94 (0.67 – 1.32)
Shikoku	0.89 (0.43 – 1.83)	1.38 (0.70 – 2.74)	1.38 (0.95 – 2.02)
Kyushu	1.25 (0.73 – 2.14)	1.30 (0.70 – 2.42)	1.14 (0.84 – 1.53)
Subspecialty			
Respirology		Ref.	
Gastroenterology		0.78 (0.49 – 1.24)	
Hematology		0.86 (0.59 – 1.27)	
Breast		0.78 (0.45 – 1.36)	
Other†		0.90 (0.50 – 1.64)	

† Other subspecialties included Urology and Head and neck cancer. Due to the small number of physicians in these two subspecialties, they were included in the "other" category; CI=Confidence interval; * <0.05, ** <0.01, *** <0.001

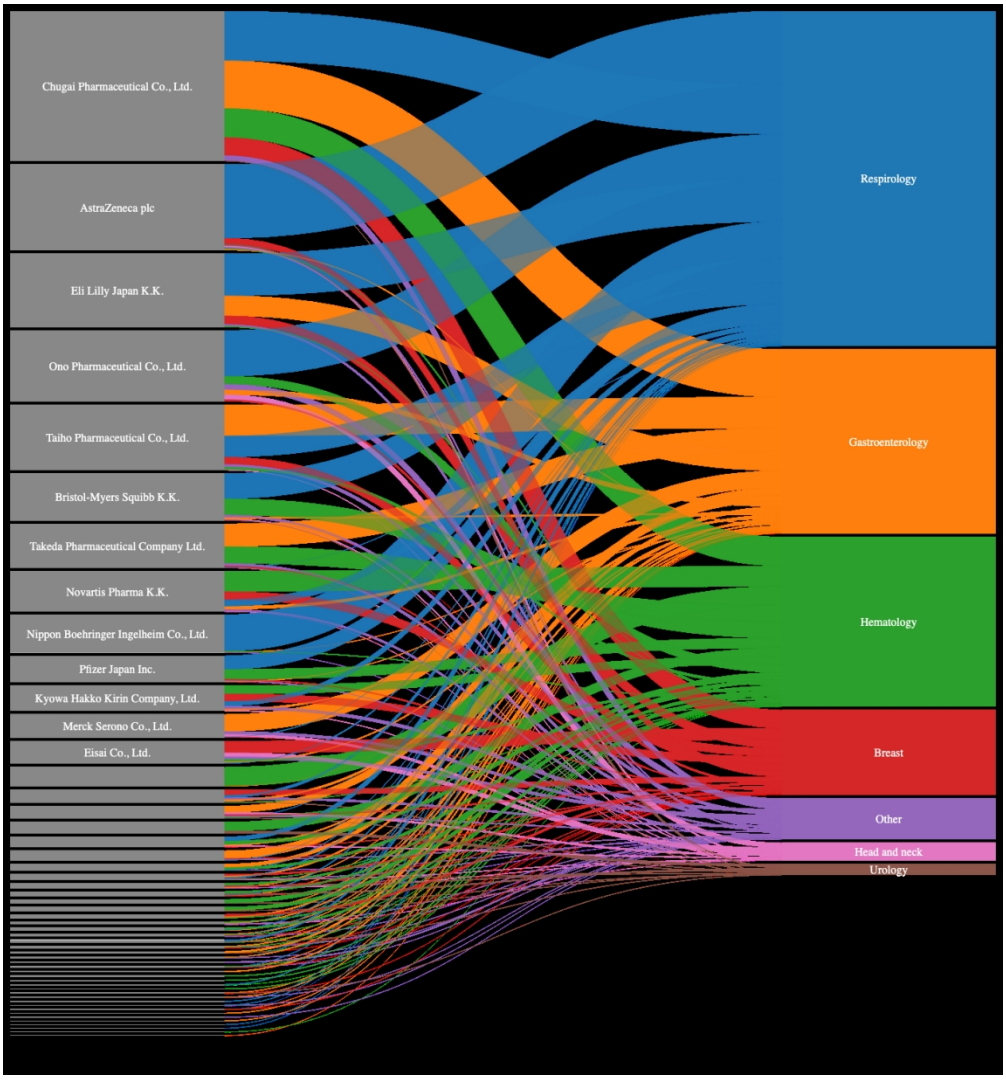

Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band color represents the payment destination specialties. Due to space limitations, names of companies with payment values of less than ¥10 million (£67.7 thousand, €80.3 thousand, $91.9 thousand) have been omitted.

493x529mm (72 x 72 DPI)

Supplementary Material 1. Seventy-eight pharmaceutical companies sampled and the start and end date of the period when the payment data was disclosed

Pharmaceutical company	Period of the payment data in 2016	
	Start date	End date
AbbVie GK	January 1, 2016	December 31, 2016
Asahi Kasei Pharma Corporation	April 1, 2016	March 31, 2017
Aska Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Astellas Pharma Inc.	April 1, 2016	March 31, 2017
AstraZeneca plc	January 1, 2016	December 31, 2016
Ayumi Pharmaceutical Corporation	April 1, 2016	March 31, 2017
Bayer Yakuhin, Ltd.	January 1, 2016	December 31, 2016
Bee Brand Medico Dental. Co., Ltd.[a]	April 1, 2016	March 31, 2017
Biofermin Seiyaku Co., Ltd.[b]	April 1, 2016	March 31, 2017
Bristol-Myers Squibb K.K.	April 1, 2016	March 31, 2017
Celgene Corporation	January 1, 2016	December 31, 2016
Chugai Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Daiichi Sankyo Company, Limited.	April 1, 2016	March 31, 2017
EA Pharma Co., Ltd.	April 1, 2016	March 31, 2017
Eisai Co., Ltd.	January 1, 2016	December 31, 2016
Eli Lilly Japan K.K.	January 1, 2016	December 31, 2016
EN Otsuka Pharmaceutical Co., Ltd.[c]	January 1, 2016	December 31, 2016
Fujimoto Pharmaceutical Corporation	July 1, 2016	June 30, 2017
Fuso Pharmaceutical Industries, Ltd.	April 1, 2016	March 31, 2017
GlaxoSmithKline K.K.	January 1, 2016	December 31, 2016
Hisamitsu Pharmaceutical Co., Inc.	March 1, 2016	February 28, 2017
Janssen Pharmaceutical K.K.	January 1, 2016	December 31, 2016

Japan Tobacco Inc.[d]	Not available	Not available
Kaken Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Kissei Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Kowa Company, Ltd.	April 1, 2016	March 31, 2017
Kracie Holdings, Ltd.	January 1, 2016	December 31, 2016
Kyorin Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Kyoto Pharmaceutical Industries, Ltd.	June 1, 2016	May 31, 2017
Kyowa Hakko Kirin Company, Ltd.	January 1, 2016	December 31, 2016
Maruho Co., Ltd.	October 1, 2016	September 30, 2017
Maruishi Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Meiji Seika Pharma Co., Ltd.	April 1, 2016	March 31, 2017
Merck Serono Co., Ltd.	January 1, 2016	December 31, 2016
Minophagen Pharmaceutical Co.	April 1, 2016	March 31, 2017
Mitsubishi Tanabe Pharma Corporation	April 1, 2016	March 31, 2017
Mochida Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
MSD K.K.	January 1, 2016	December 31, 2016
Mylan Seiyaku Ltd.	January 1, 2016	December 31, 2016
Nihon Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Nippon Boehringer Ingelheim Co., Ltd.	January 1, 2016	December 31, 2016
Nippon Chemiphar Co., Ltd.	January 1, 2016	December 31, 2016
Nippon Kayaku Co., Ltd.	April 1, 2016	March 31, 2017
Nippon Shinyaku Co., Ltd.	April 1, 2016	March 31, 2017
Nippon Zoki Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Novartis Pharma K.K.	January 1, 2016	December 31, 2016
Novo Nordisk Pharma Ltd.	January 1, 2016	December 31, 2016
Ono Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Otsuka Holdings Co., Ltd.[e]	January 1, 2016	December 31, 2016

Otsuka Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Otsuka Pharmaceutical Factory, Inc.[f]	January 1, 2016	December 31, 2016
Pfizer Japan Inc.	December 1, 2015	November 30, 2016
POLA-Pharma.	January 1, 2016	December 31, 2016
Research Institute for Microbial Diseases	April 1, 2016	March 31, 2017
Sanofi K.K.	January 1, 2016	December 31, 2016
Santen Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Sanwa Kagaku Kenkyusho Co., Ltd.	April 1, 2016	March 31, 2017
Seikagaku Corporation	April 1, 2016	March 31, 2017
Senju Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Shionogi & Co., Ltd.	April 1, 2016	March 31, 2017
Shire Japan K.K.	January 1, 2016	December 31, 2016
Sumitomo Dainippon Pharma Co., Ltd.	April 1, 2016	March 31, 2017
Taiho Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Taisho Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Taisho Toyama Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Takeda Pharmaceutical Company Ltd.	April 1, 2016	March 31, 2017
Teijin Pharma Limited.	April 1, 2016	March 31, 2017
Teikoku Seiyaku Co., Ltd.	January 1, 2016	December 31, 2016
Terumo Corporation	April 1, 2016	March 31, 2017
Toa Eiyo Ltd.	April 1, 2016	March 31, 2017
Toray Industries, Inc.	April 1, 2016	March 31, 2017
Torii Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Toyama Chemical Co., Ltd.	April 1, 2016	March 31, 2017
Tsumura & Co.	April 1, 2016	March 31, 2017
UCB Japan Co., Ltd.	January 1, 2016	December 31, 2016
Wakamoto Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017

Yakult Honsha Company, Limited.	April 1, 2016	March 31, 2017
Zeria Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017

[a] Affiliated company of Ono Pharmaceutical Co., Ltd.; [b] affiliated company of Taisho Pharmaceutical Co., Ltd.; [c] affiliated company of Otsuka Pharmaceutical Co., Ltd.; [d] the company left the Japan Pharmaceutical Manufacturers Association on March 31, 2018; [e] affiliated company of Otsuka Pharmaceutical Co., Ltd.; [f] affiliated company of Otsuka Pharmaceutical Co., Ltd.; [g] affiliated company of Taisho Pharmaceutical Co., Ltd. and Toyama Chemical Co., Ltd.

Supplementary Material 2. Monetary value of payment (¥ [£]) in each company according to oncology subspecialty

Pharmaceutical company	Respirology	Gastroenterology	Hematology	Breast	Head and neck	Urology	Other	Total
Chugai Pharmaceutical Co., Ltd.	24,545,685 [166,186]	23,656,984 [160,169]	14,432,072 [99,807]	8,958,305 [60,652]	0 [0]	229,104 [1,551]	2,554,519 [17,295]	74,376,669 [503,566]
AstraZeneca plc	36,577,758 [247,649]	495,596 [3,355]	501,165 [3,466]	2,882,255 [19,514]	623,673 [4,223]	890,960 [6,032]	573,556 [3,883]	42,544,963 [288,050]
Eli Lilly Japan K.K.	20,798,349 [140,815]	9,967,102 [67,482]	556,850 [3,851]	4,145,014 [28,064]	0 [0]	0 [0]	957,782 [6,485]	36,425,097 [246,615]
Ono Pharmaceutical Co., Ltd.	22,619,251 [153,143]	2,504,140 [16,954]	3,897,950 [26,957]	924,372 [6,258]	2,383,319 [16,136]	0 [0]	2,706,291 [18,323]	35,035,323 [237,206]
Taiho Pharmaceutical Co., Ltd.	10,524,465 [71,256]	15,397,224 [104,247]	1,280,755 [8,857]	3,530,431 [23,903]	222,740 [1,508]	0 [0]	1,436,673 [9,727]	32,392,288 [219,311]
Bristol-Myers Squibb K.K.	12,428,895 [84,150]	946,645 [6,409]	8,007,520 [55,377]	33,411 [226]	356,384 [2,413]	278,426 [1,885]	1,158,248 [7,842]	23,209,529 [157,140]
Takeda Pharmaceutical Company Ltd.	136,826 [926]	11,176,272 [75,669]	8,354,702 [57,778]	523,439 [3,544]	57,276 [388]	171,829 [1,163]	1,256,893 [8,510]	21,677,237 [146,765]
Novartis Pharma K.K.	3,374,513 [22,847]	1,470,084 [9,953]	10,056,724 [69,549]	4,052,615 [27,438]	77,959 [528]	0 [0]	954,371 [6,462]	19,986,266 [135,317]
Nippon Boehringer Ingelheim Co., Ltd.	17,908,315 [121,248]	111,370 [754]	445,480 [3,081]	0 [0]	0 [0]	0 [0]	77,959 [528]	18,543,124 [125,546]

Pfizer Japan Inc.	6,683,175 [45,248]	332,201 [2,249]	4,834,111 [33,431]	638,311 [4,322]	0 [0]	22,910 [155]	538,396 [3,645]	13,049,104 [88,349]
Kyowa Hakko Kirin Company, Ltd.	2,338,770 [15,835]	902,097 [6,108]	3,975,910 [27,496]	3,669,644 [24,845]	111,370 [754]	0 [0]	1,470,089 [9,953]	12,467,880 [84,414]
Merck Serono Co., Ltd.	334,110 [2,262]	8,397,065 [56,852]	0 [0]	33,411 [226]	1,258,481 [8,521]	0 [0]	1,369,851 [9,275]	11,392,918 [77,136]
Eisai Co., Ltd.	445,480 [3,016]	523,439 [3,544]	1,180,522 [8,164]	5,791,243 [39,209]	1,948,977 [13,196]	0 [0]	1,380,988 [9,350]	11,270,649 [76,308]
Celgene Corporation	0 [0]	103,120 [698]	9,376,553 [64,845]	0 [0]	0 [0]	0 [0]	0 [0]	9,479,673 [64,182]
Daiichi Sankyo Company, Limited.	1,180,527 [7,993]	915,086 [6,196]	222,740 [1,540]	2,615,204 [17,706]	0 [0]	389,796 [2,639]	973,096 [6,588]	6,296,449 [42,630]
Bayer Yakuhin, Ltd.	77,959 [528]	3,164,949 [21,428]	412,069 [2,850]	701,634 [4,750]	863,118 [5,844]	278,425 [1,885]	612,535 [4,147]	6,110,689 [41,372]
Janssen Pharmaceutical K.K.	0 [0]	0 [0]	4,387,980 [30,346]	0 [0]	0 [0]	1,252,917 [8,483]	0 [0]	5,640,897 [38,192]
MSD K.K.	2,013,013 [13,629]	545,715 [3,695]	1,748,510 [12,092]	278,425 [1,885]	529,009 [3,582]	0 [0]	0 [0]	5,114,672 [34,629]
Yakult Honsha Company, Limited.	288,740 [1,955]	3,764,259 [25,486]	0 [0]	381,548 [2,583]	0 [0]	0 [0]	381,548 [2,583]	4,816,095 [32,607]
Sumitomo Dainippon Pharma Co., Ltd.	278,425 [1,885]	1,626,004 [11,009]	1,069,152 [7,394]	0 [0]	0 [0]	0 [0]	77,959 [528]	3,051,540 [20,660]

Nippon Kayaku Co., Ltd.	662,651 [4,486]	668,220 [4,524]	167,055 [1,155]	800,124 [5,417]	111,370 [754]	222,740 [1,508]	222,740 [1,508]	2,854,900 [19,329]
Sanofi K.K.	0 [0]	312,500 [2,116]	890,000 [6,155]	370,000 [2,505]	100,000 [677]	550,000 [3,724]	50,000 [339]	2,272,500 [15,386]
Astellas Pharma Inc.	390,000 [2,640]	100,000 [677]	900,000 [6,224]	100,000 [677]	0 [0]	700,000 [4,739]	0 [0]	2,190,000 [14,827]
Nippon Shinyaku Co., Ltd.	0 [0]	0 [0]	1,804,194 [12,477]	0 [0]	0 [0]	111,370 [754]	0 [0]	1,915,564 [12,969]
Asahi Kasei Pharma Corporation	0 [0]	114,552 [776]	1,659,413 [11,476]	0 [0]	0 [0]	111,370 [754]	0 [0]	1,885,335 [12,765]
AbbVie GK,	0 [0]	523,439 [3,544]	245,014 [1,694]	1,046,885 [7,088]	0 [0]	0 [0]	0 [0]	1,815,338 [12,291]
Otsuka Holdings Co., Ltd.e	100,000 [677]	440,000 [2,979]	550,000 [3,804]	0 [0]	46,286 [313]	0 [0]	200,000 [1,354]	1,336,286 [9,047]
Shionogi & Co., Ltd.	288,736 [1955]	329,984 [2,234]	309,360 [2,139]	206,240 [1,396]	0 [0]	0 [0]	103,120 [698]	1,237,440 [8,378]
Kyorin Pharmaceutical Co., Ltd.	845,584 [5,725]	72,184 [489]	72,184 [499]	0 [0]	0 [0]	206,241 [1,396]	0 [0]	1,196,193 [8,099]
Teijin Pharma Limited.	170,000 [1,151]	70,000 [474]	850,000 [5,878]	0 [0]	0 [0]	0 [0]	0 [0]	1,090,000 [7,380]
Mochida Pharmaceutical Co., Ltd.	0 [0]	378,658 [2,564]	267,288 [1,848]	111,370 [754]	0 [0]	0 [0]	189,329 [1,282]	946,645 [6,409]
Tsumura & Co.	0 [0]	779,590 [5,278]	55,685 [385]	55,685 [377]	0 [0]	0 [0]	0 [0]	890,960 [6,032]
Terumo Corporation	110,440 [748]	430,716 [2,916]	0 [0]	0 [0]	0 [0]	0 [0]	110,440 [748]	651,596 [4,412]

Kowa Company, Ltd.	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	556,851 [3,770]	556,851 [3,770]
Meiji Seika Pharma Co., Ltd.	103,120 [698]	51,560 [349]	278,424 [1,925]	51,560 [349]	0 [0]	0 [0]	72,184 [489]	556,848 [3,770]
Zeria Pharmaceutical Co., Ltd.	0 [0]	445,480 [3,016]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	445,480 [3,016]
Sanwa Kagaku Kenkyusho Co., Ltd.	0 [0]	0 [0]	445,480 [3,081]	0 [0]	0 [0]	0 [0]	0 [0]	445,480 [3,016]
Novo Nordisk Pharma Ltd.	0 [0]	0 [0]	360,925 [2,496]	0 [0]	0 [0]	0 [0]	0 [0]	360,925 [2,444]
Taisho Toyama Pharmaceutical Co., Ltd.	311,836 [2,111]	0 [0]	33,411 [231]	0 [0]	0 [0]	0 [0]	0 [0]	345,247 [2,337]
Aska Pharmaceutical Co., Ltd.	0 [0]	111,370 [754]	0 [0]	77,959 [528]	0 [0]	111,370 [754]	0 [0]	300,699 [2,036]
Nippon Chemiphar Co., Ltd.	0 [0]	167,055 [1,131]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]	278,425 [1,885]
Ayumi Pharmaceutical Corporation	226,864 [1,536]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	226,864 [1,536]
Kissei Pharmaceutical Co., Ltd.	111,370 [754]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]	222,740 [1,508]
Shire Japan K.K	0 [0]	0 [0]	222,740 [1,540]	0 [0]	0 [0]	0 [0]	0 [0]	222,740 [1,508]
Teijin Pharma Limited.	190,000 [1,286]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	190,000 [1,286]
Hisamitsu Pharmaceutical Co., Inc.	22,274 [151]	33,411 [226]	0 [0]	111,370 [754]	0 [0]	0 [0]	0 [0]	167,055 [1,131]
Sumitomo Dainippon Pharma Co., Ltd.	0 [0]	0 [0]	167,055 [1,155]	0 [0]	0 [0]	0 [0]	0 [0]	167,055 [1,131]
EA Pharma Co., Ltd.	0 [0]	154,680 [1,047]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	154,680 [1,047]
Shire Japan K.K	0 [0]	0 [0]	111,370 [770]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]

Kracie Holdings, Ltd.	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]	103,120 [698]
Maruho Co., Ltd.	0 [0]	103,120 [698]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]
Mitsubishi Tanabe Pharma Corporation	77,959 [528]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959 [528]
GlaxoSmithKline K.K.	55,685 [377]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	55,685 [377]
Nihon Pharmaceutical Co., Ltd.	0 [0]	0 [0]	55,685 [385]	0 [0]	0 [0]	0 [0]	0 [0]	55,685 [377]
EN Otsuka Pharmaceutical Co., Ltd.	0 [0]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	33,411 [226]
All	166,220,775 [1,125,395]	91,319,282 [618,275]	84,186,048 [582,200]	42,090,455 [284,973]	8,689,962 [58,835]	5,527,458 [37,424]	20,311,278 [137,517]	418,345,258 [2,832,398]

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

Supplementary Material 3. List of oncology drugs with Japanese domestic sales of at least ¥5 billion [£33.9 million] in 2016

Pharmaceutical company	Drug name	2016 Sales (Billion, ¥)†	2016 Sales (Million, £)†	Respirology	Gastroenterology	Hematology	Breast	Urology	Head and neck	Other
Astellas Pharma Inc.	Enzalutamide	23.4	158.4	No	No	No	No	Yes	No	No
Chugai Pharmaceutical Co., Ltd.	Bevacizumab	92.1	623.6	Yes	Yes	No	Yes	No	No	Yes
Chugai Pharmaceutical Co., Ltd.	Trastuzumab	34.1	230.9	No	Yes	No	Yes	No	No	No
Chugai Pharmaceutical Co., Ltd.	Rituximab	32.1†	217.3†	No	No	Yes	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Capecitabine	12.3	83.3	No	Yes	No	Yes	No	No	No
Chugai Pharmaceutical Co., Ltd.	Pertuzumab	11.9	80.6	No	No	No	Yes	No	No	No
Chugai Pharmaceutical Co., Ltd.	Alectinib	11.9	80.6	Yes	No	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Erlotinib	11.5	77.9	Yes	No	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Trastuzumab Emtansine	8.3	56.2	No	No	No	Yes	No	No	No
Daiichi Sankyo Co., Ltd.	Denosumab	13.9	94.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Eisai Co., Ltd.	Eribulin	7.8	52.8	No	No	No	Yes	No	No	Yes
Eli Lilly Japan K.K.	Pemetrexed	37.3	252.5	Yes	No	No	No	No	No	No
Eli Lilly Japan K.K.	Ramucirumab	28.9	195.7	Yes	Yes	No	No	No	No	No

Nippon Boehringer lngelheim Co., Ltd.	Afatinib	8.7	58.9	Yes	No	No	No	No	No	No
Novartis International AG	Imatinib	27.5	186.2	No	Yes	Yes	No	No	No	No
Novartis International AG	Nilotinib	20.7	140.1	No	No	Yes	No	No	No	No
Novartis International AG	Everolimus	15.1†	102.2†	Yes	Yes	No	Yes	Yes	No	No
Ono Pharmaceutical Co., Ltd.	Nivolumab	103.9	703.5	Yes	No	Yes	No	Yes	Yes	Yes
Taiho Pharmaceutical Co., Ltd.	Tegafur/Gimeracil/Oteracil	26.9	182.1	Yes	Yes	No	Yes	No	Yes	No
Taiho Pharmaceutical Co., Ltd.	nab-Paclitaxel	20.7	140.1	Yes	Yes	No	Yes	No	No	No
Taiho Pharmaceutical Co., Ltd.	Calcium Folinate	9.7	65.7	No	Yes	No	No	No	No	No
Taiho Pharmaceutical Co., Ltd.	Tegafur, Uracil	6.5	44.0	Yes	Yes	No	Yes	Yes	Yes	Yes
Takeda Pharmaceutical Co., Ltd.	Leuprorelin	48.6†	329†	No	No	No	Yes	Yes	No	No
Takeda Pharmaceutical Co., Ltd.	Panitumumab	18.8	127.3	No	Yes	No	No	No	No	No
Yakult Honsha Co., Ltd.	Oxaliplatin	18.4	124.6	No	Yes	No	No	No	No	No

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1; A coverage under the Japanese National Health Insurance scheme in specific oncology subspecialty was considered by the end of the fiscal year of 2016 (March 31, 2017); † The sales includes that used for conditions other than cancer.

Supplementary Material 4. Newly-approved oncology drugs and drugs with added indications during the fiscal years of 2015 and 2016.

Pharmaceutical company	Drug name	Date of approval	Type of approval	Type of cancer
AstraZeneca plc	Vandetanib	September 28, 2015	New approval	Thyroid cancer
AstraZeneca plc	Osimertinib	March 28, 2016	New approval	Non-small cell lung cancer
Bayer Yakuhin, Ltd.	Sorafenib	February 29, 2016	Added indication	Thyroid cancer
Bayer Yakuhin, Ltd.	Xofigo	March 28, 2016	New approval	Prostate cancer
Bristol-Myers Squibb K.K.	Ipilimumab	July 3, 2015	New approval	Melanoma
Bristol-Myers Squibb K.K.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
Bristol-Myers Squibb K.K.	Elotuzumab	September 28, 2016	New approval	Multiple myeloma
Celgene Corporation	Lenalidomide	December 21, 2015	Added indication	Multiple myeloma
Celgene Corporation	Lenalidomide	March 2, 2017	Added indication	Adult T-cell leukemia
Chugai Pharmaceutical Co., Ltd.	Capecitabine	November 20, 2015	Added indication	Gastric cancer
Chugai Pharmaceutical Co., Ltd.	Bevacizumab	May 23, 2016	Added indication	Cervical cancer
Chugai Pharmaceutical Co., Ltd.	Capecitabine	August 26, 2016	Added indication	Rectal cancer

Eisai Co., Ltd.	Eribulin	February 29, 2016	Added indication	Sarcoma
Eli Lilly Japan K.K.	Ramucirumab	May 23, 2016	Added indication	Colorectal cancer
Eli Lilly Japan K.K.	Ramucirumab	June 20, 2016	Added indication	Non-small cell lunc cancer
GlaxoSmithKline K.K.	Lapatinib	November 20, 2015	Added indication	Breast cancer
Janssen Pharmaceutical K.K.	Ibrutinib	March 28, 2016	New approval	Chronic lymphocytic leukemia
Janssen Pharmaceutical K.K.	Bortezomib	June 26, 2015	Added indication	Mantle cell lymphoma
Janssen Pharmaceutical K.K.	ibrutinib	December 2, 2016	Added indication	Mantle cell lymphoma
Meiji Seika Pharma Co., Ltd.	Talaporfin	May 26, 2015	Added indication	Esophageal cancer
Minophagen Pharmaceutical Co.	Bexarotene	January 22, 2016	New approval	Cutaneous T cell lymphoma
MSD K.K.	Peginterferon Alfa-2b	May 26, 2015	Added indication	Melanoma
MSD K.K.	Pembrolizumab	September 28, 2016	New approval	Melanoma
MSD K.K.	Pembrolizumab	December 19, 2016	Added indication	Non-small cell lung cancer
Mylan Seiyaku Ltd.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
Nippon Kayaku Co., Ltd.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
Nippon Kayaku Co., Ltd.	Nogitecan	November 20, 2015	Added indication	Cervical cancer
Novartis Pharma K.K.	Panobinostat	July 3, 2015	New approval	Multiple myeloma

Novartis Pharma K.K.	Ruxolitinib	September 24, 2015	Added indication	Polycythemia vera
Novartis Pharma K.K.	Dabrafenib	March 28, 2016	New approval	Melanoma
Novartis Pharma K.K.	Trametinib	March 28, 2016	New approval	Melanoma
Novartis Pharma K.K.	Ceritinib	March 28, 2016	New approval	Non-small cell lung cancer
Novartis Pharma K.K.	Everolimus	August 26, 2016	Added indication	Neuro-endocrine tumor
Ono Pharmaceutical Co., Ltd.	Nivolumab	February 29, 2016	Added indication	Melanoma
Ono Pharmaceutical Co., Ltd.	Nivolumab	December 17, 2015	Added indication	Non-small cell lung cancer
Ono Pharmaceutical Co., Ltd.	Carfilzomib	July 4, 2016	New approval	Multiple myeloma
Ono Pharmaceutical Co., Ltd.	Nivolumab	August 26, 2016	Added indication	Renal cell cancer
Ono Pharmaceutical Co., Ltd.	Nivolumab	December 2, 2016	Added indication	Hodgkin lymphoma
Ono Pharmaceutical Co., Ltd.	Nivolumab	March 24, 2017	Added indication	Head and neck cancer
Otsuka Pharmaceutical Co., Ltd.	Ponatinib	September 28, 2016	New approval	Chronic myelogenous leukemia
Sanofi K.K.	Plerixafor	December 19, 2016	New approval	Multiple myeloma Non-Hodgkin lymphoma Hodgkin lymphoma
Sanofi K.K.	Aflibercept Beta	March 30, 2017	New approval	Colorectal cancer

Shionogi & Co., Ltd.	Cyclophosphamide	June 26, 2015	Added indication	Malignant lymphoma
Shionogi & Co., Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
Taiho Pharmaceutical Co., Ltd.	Trabectedin	September 28, 2015	New approval	Sarcoma
Takeda Pharmaceutical Company Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
Takeda Pharmaceutical Company Ltd.	Leuprorelin	September 28, 2015	New approval	Prostate cancer Breast cancer
Takeda Pharmaceutical Company Ltd.	Ixazomib	March 30, 2017	New approval	Multiple myeloma
Yakult Honsha Company, Limited.	Oxaliplatin	November 20, 2015	Added indication	Gastric cancer

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-10
Objectives	3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	10-14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	10-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	13-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-14
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-14
		(*b*) Describe any methods used to examine subgroups and interactions	13-14
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	13-14
		(*e*) Describe any sensitivity analyses	13-14

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	15
		(b) Give reasons for non-participation at each stage	15
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	16-18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	18
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	27-28
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-25
Generalisability	21	Discuss the generalisability (external validity) of the study results	25-26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Pharmaceutical payments to certified oncology specialists in Japan in 2016: a retrospective observational cross-sectional analysis

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Title:

Pharmaceutical payments to certified oncology specialists in Japan in 2016: a retrospective observational cross-sectional analysis

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Abstract (296 words)

Objective: This study investigated payments made by pharmaceutical companies to oncology specialists in Japan, what the payments were for, and whether the receipt of such payments contravened any Conflict of Interest (COI) regulations.

Design, Setting, and Participants: Payment data to physicians, as reported by all pharmaceutical companies belonging to the Japan Pharmaceutical Manufacturers Association (JPMA), were retrospectively extracted for 2016. Of the named individual recipients of payments, all certified oncologists were identified, using certification data from the Japanese Society of Medical Oncology (JSMO). The individual specializations of each of the oncologists was also identified.

Outcome: Payments to individual cancer specialists and what they were for were identified. Factors associated with receipt of higher value payments and payment flows to specialties were determined. Companies selling oncology drugs with annual sales of ≥¥5 billion [£33.9 million, €40.2 million, $46.0 million] (high revenue generating drugs) were identified.

Results: In total, 59 companies made at least one payment to oncologists. Of the 1080 oncology specialists identified, 763 (70.6%) received at least one payment, while 317 received no payment. Of the 763, some 142 (13.1%) receiving at least ¥1 million [£6,800, €8,000, $9,200] accounted for 71.5% of the total. After adjustment of covariates, working for university hospitals and cancer hospitals and male gender were

key factors associated with larger monetary payments. Payments preferentially targeted on cancer specialties using high revenue generating drugs. The JSMO has its own COI policy for its members but the policy did not mention any specific guidelines for certified oncology specialists.

Conclusion: Financial relationships were identified and quantified between pharmaceutical companies and oncology specialists, but the extent and worth varied significantly. Given the frequency and amounts of money involved in such linkages, it would be beneficial for specific COI regulations to be developed and policed for oncologists.

Keywords: conflict of interest; oncology specialist; Japan; industry payment; Japanese Society of Medical Oncology

Article summary (Strengths and limitations of this study):

- ✓ We considered oncology specialists certified by the Japan Society of Medical Oncology, one of the largest professional medical associations in Japan's clinical oncology field.

- ✓ The authors independently organized payment data for speaking, writing, and consulting work, as published by the major pharmaceutical companies, and created a single uniform payment database.
- ✓ Accuracy of the affiliations and subspecialties of some oncology specialist in the study year (2016) were estimated using the data on relevant websites and other data sources on the Internet, possibly causing some measurement errors in these variables.
- ✓ This study only covered limited types of payment data in the single year (2016), which hampered a comprehensive and/or longitudinal analysis of the type and value of the payments among the oncology specialists.

Word count: 4,964

Introduction

Increasing global attention is being paid with respect to how pharmaceutical companies (Pharma) operate and their relationships with regard to payments they make to doctors working in national health systems. There is growing concern that specialised

physicians receiving financial payments from Pharma commercially connected with their field of expertise may be inadvertently or unethically being influenced and that their impartiality and ability to act in the best interests of their patients is being compromised. The approval earlier this year by the US Federal Drugs Administration (FDA) of anasemnogene abeparvovec-xioi (Zolgensma®☐), a gene therapy for children less than 2 years old with spinal muscular atrophy which is now the most expensive drug on the market, illustrates the amounts of money that are involved. If a physician prescribes Zolgensma treatment, and a single administration is all that is required, it costs $2.1 million (£1.6 million, €1.9 million, ¥231.2 million) per patient. In Japan, a new treatment for leukemia and other hematologic cancers was approved in May which will cost ¥33.5 million (£226,800, €269,000, $307,800). The drug, Tisagenlecleucel (Kymriah®), manufactured and marketed by Novartis Pharma KK, is the most expensive drug on the Japanese market and is covered under Japan's national health insurance. In view of the sums of money involved and the possibility of corruption creeping into the system, there is an increasing need for transparency with respect to all forms of payment, or gifts of any kind, being dispensed by Pharma to physicians. According to the World Medical Association (WMA), "although the cooperation between physicians and commercial enterprises may lead to significant

advances in medicine, including the development of new drugs and treatments, it may also result in a conflict of interest (COI) between commercial enterprises and physicians that may have adverse effects on patients' care and the reputation of physicians". Consequently, medical and governmental facilities worldwide are considering steps to help create transparency in the relationship between physicians and the pharmaceutical industry, as exemplified by the USA's Physician Payments Sunshine Act, enacted in 2010, and the US government's Open Payments Database (https://openpaymentsdata.cms.gov).[1 2] In Japan, members of the Japan Pharmaceutical Manufacturers Association (JPMA) are attempting to improve the transparency and acceptability of the relationship between corporate activities of Pharma and medical institutions and individual physicians and, in 2015, the JPMA introduced a self-regulatory Guideline for all its members to promote clarity and deeper understanding of the beneficial contribution that Pharma makes to medicine and pharmacy, and so that Pharma activities are conducted with high ethical standards and for maximum benefit to patients.

Cancer has been the leading cause of mortality in Japan since 1981. In 2016, there were 372,986 cancer deaths in Japan, with malignant neoplasms costing the nation an

estimated ¥3.6 trillion [£24.4 billion, €28.9 billion, $33.1 billion] in medical expenditure. In 2016, lung cancer was the leading cause of cancerous deaths (52,430) in males, followed by gastric cancer (29,854) and colorectal cancer (27,026), while colorectal cancer was the leading cause of cancerous death in females (23,073), followed by lung cancer (21,408) and colorectal cancer (17,405).[3] The risk factors for cancer are diverse, including tobacco use, infection, obesity, radiation exposure, reproductive and hormonal factors, and other environmental and occupational pollutants and carcinogens.[4] In Japan, principally because of its ageing population, cancer rates are forecast to continue to rise for the foreseeable future.[3]

For the pharmaceutical industry, medical and therapeutic practice generates substantial income, allowing it exploit various opportunities to accomplish the goal of the maximization of profits.[5-7] From the 1950s, the main business model of the Pharma was the production of low-price drugs to treat diseases and conditions that were primarily chronic and prevalent (e.g. hypertension and diabetes).[8-10] Following advances in drug development against infectious and chronic diseases, cancer became an ever-increasing and major problem, with 17.2 million incidents and 213.2 million cancer-associated disability-adjusted life-years (DALY) lost during 1990-2016 worldwide.[11] Pharma

therefore adopted a new business model, the discovery and development of anticancer agents that could be sold at extremely high price, but usually for short treatment durations.[5-7] This guaranteed a hefty profit in a short timeframe - provided that the drugs would be prescribed and used - while imposing an extraordinarily high cost on patients and health systems.[5-7 12]

Physicians remain paramount decision-makers on the demand-side of the pharmaceutical market. It is known that even subtle financial interactions between physicians and a pharmaceutical company can affect their prescribing behavior,[13-18] and so could encourage irrational or preferential use of a company's drug. Perhaps unsurprisingly, given the cost of anticancer drugs, oncologists have latterly become primary targets for approaches from companies with high-cost anticancer products to sell. Indeed, significant financial relationships between such companies and the authors of the oncology Clinical Practice Guidelines (CPGs) have been reported both in the United States and Japan.[19 20] Given these far from ideal circumstances, there has been a growing need for intervention, in the form of policy implementation and education about the implications of these interactions, to help protect physicians, patients, institutions and the companies themselves.[15-18]

Although Japan has the world's third largest pharmaceutical market, with annual sales of $76 billion in 2017,[21] its overall scale has been declining at approximately 2% annually.[22] To maintain sales in these competitive and tightening markets, forceful advertisement of high-price products, namely novel oncology drugs, has become increasingly important for pharmaceutical companies. Indeed, sales of oncology drugs have recently been rising in Japan, exceeding ¥1 trillion [£6.8 billion, €8.0 billion, $9.2 billion] for the first time in 2016.[23] Furthermore, sales are predicted to increase 1.5–fold in the next decade with the increasing application of immunotherapy in clinical practice.[23] It would therefore be reasonable to assume that pharmaceutical companies will increasingly deploy marketing measures and incentives targeting oncology specialists for the immediate and foreseeable future.

In Japan, the JPMA encompasses a majority of companies that manufacture brand name drugs. Its members accounted for 80.8% of total pharmaceutical sales in Japan in 2015.[24] In 2011, the JPMA published a transparency Guideline requiring all member companies to disclose all payments for speaking, writing and consulting made to all individuals, specifying their names and affiliations.[25] The Guideline was updated in

2015 and made more comprehensive. The aim was to improve the transparency of linkages between pharmaceutical companies and physicians, as in the Open Payments Database in the United States.[1 2] The 2015 revised JPMA Guideline obliges Pharma to itemize payments made for 1) Research & Development; 2) Academic support; 3) Lecturing/writing/consultancy work; 4) Expenses related to provision of information and 5) Expenses for hospitality, etc. However, the disclosure format, whereby companies involved published the required data on their own individual websites, has differed among and between companies and the aggregated, standardized payment data have not been readily available.[26] As a result, an easy examination of company/physicians links and payments in a meaningful way has proved almost impossible.

The aims of the current study were: 1) to understand and evaluate the characteristics and distributions of financial payments made by pharmaceutical companies to oncology specialists: 2) to examine whether or not pharmaceutical companies may be making payments to help promote sales of their own products; and 3) to elucidate what Japanese oncology specialists are obliged to disclose with respect to any COI.

Methods

Study setting and participants

The Japan Society of Medical Oncology (JSMO), with over 9154 general members, is the primary professional medical society in the clinical oncology field in Japan. The JSMO began operating a specialty registration system for members in 2004, which required JSMO members wishing to be certified to meet specific requirements for both oncology care and academic achievement. Only after passing the requisite examination, could they become board-certified oncology specialists, with renewal of certification being required every five years. All 1,081 oncology specialists certified by the JSMO as of April 1st, 2016, were included in this study.

Sources of Payment Data

The sources of the payment data were the websites of 78 pharmaceutical companies that were members of the JPMA in fiscal 2016. These companies were required to publish data of payments made to physicians and other researchers annually under the transparency guidelines of the JPMA. They were categorized into 71 active JPMA members, six affiliated entities of these companies, and one past member. The

companies included in this study, plus their payment data, are listed in Supplementary Material 1.

We obtained each company's data and organized them into a unified, easy-to-compare database. This was done because no data was published as a spreadsheet. Consequently, data with differing character codes were converted into a spreadsheet format and data with no character codes were converted into text files using an Optical Character Reader. Moreover, where data was protected against facsimile or reproduction, we used FullShot10 software (Inbit, CA, USA) to scan photos of the data and converted the data into text files. The accuracy of the re-organized data was confirmed by comparing it with the original data. The database included physicians' names, their main institutional affiliation, payments received, the form of the payments, and the total amount paid. The form of payment was categorized into three types; payment for speaking engagements, payment for writing or publication work, and consulting fees. For the purposes of this study, we converted Japanese yen (¥) to Pounds Sterling (£), Euro (€), and US dollars ($), using the average monthly exchange rate for 2016, namely ¥147.7 per £1, ¥124.5 per €1 and ¥108.8 per US$1.

Data collection

We examined payment data for all oncology specialists included in this study. We extracted their working institutions and regional locations, along with the year of their certification by the JSMO. We further confirmed the accuracy of such information, collating data from institutional websites and other sources. We determined the sex of all the oncologists, using data from Japan's Ministry of Health, Labour and Welfare,[27] institutional websites and other sources. We further estimated the primary cancer specialty (respirology, gastroenterology, hematology, breast, etc.) of all oncologists included in the study. We also determined the COI policy of the JSMO prevailing at the time.

Data analysis

To examine the characteristics and distributions of payments, we performed descriptive analyses of the data on an individual oncology specialist and pharmaceutical company basis. We then summarized the characteristics of oncology specialists according to the total monetary value of the payment they received, dividing the patients into the three groups; ¥1 million [£6,800, €8,000, $9,200] or above (High-payment group (HPG)); ¥1 – 1 million (Low-payment group (LPG)), and ¥0 (No-payment group (NPG)). In

general, ¥1 million is approximately 25% of the median annual income of a Japanese citizen.[28]

Using a multivariate negative binomial regression model, we subsequently examined possible factors associated with the monetary value of the payment to each individual, with sex, institutional place of work, regional working locations, year of experience after board certification, and cancer specialty as covariates. The payment data was rounded down as a unit of ¥1 million. Since the payment of those receiving less than ¥1 million (Low-payment and No-payment Groups) was regarded as zero in the regression analysis, among this group we further examined possible factors associated with the monetary value of any payment using the same model adopted for the overall population. For this analysis, the payment data was rounded down as a unit of ¥100,000 [£677, €803, $919].

For more detailed examination, a Sankey diagram was created to illustrate the distribution of payments to each cancer specialty on an individual company basis. The Sankey diagram is a flow diagram, where band width proportionally represents the flow quantity.[29] Payment values from individual companies, according to cancer specialty,

are depicted in the bands in the diagram, width being proportional to the total amount of the payment. In addition, to see whether the payment was linked to any specific oncology drugs, we examined such drugs with annual Japanese domestic sales of ¥5 billion [£33.9 million, €40.2 million, $46.0 million] or above (high revenue generating drugs) in fiscal 2016, and if each drug was covered under the Japanese National Health Insurance scheme in specific oncology subspecialty by the end of the same fiscal year (March 31, 2017). We further examined newly-approved drugs and drugs with a new indication added during the fiscal years of 2015 and 2016 (April 1, 2015 to March 31, 2017).

Human subject involvement

The present study is a retrospective analysis of existing databases and public domain information. No patients or any other individuals other than oncology specialists identified in the public domain, and whose names are not identified in this report, were included in the study.

Results

The JSMO had over 9,000 members at the time the study was undertaken, with 1081 physicians having been Board Certified as oncology specialists. We excluded one oncologist whose professional affiliation we were unable to confirm, and he did not receive any payment from the pharmaceutical companies. Thus, we included a total of 1,080 specialist oncologists in our analyses.

Table 1 summarizes the details of certified oncologists and payments from Japanese pharmaceutical firms. Of the 1,080 individuals involved, 907 were men (84.0%) and 173 (16.0%) were women. Of the total, 442 (40.9%), 183 (16.9%), and 455 (42.1%) worked for university hospitals, cancer hospitals, and other institutions, respectively. In 2016, the most common specialty was respirology (285, 26.4%), followed by gastroenterology (278, 25.7%) and hematology (250, 23.2%).

A total of 7,325 payments were recorded, the total monetary value being ¥585,453,314 [£3,963,800, €4,702,436, $5,381,005]. Of this total, ¥467,802,690 [£3,167,249, €3,757,451, $4,299,657] was for speaking engagements, ¥94,682,807 [£641,048, €760,504, $870,246] was for consulting services, and ¥22,266,186 [£150,753, €178,845, $204,652] was paid for writing work. The median monetary value and count of an

individual payment was ¥120,016 [£813, €964, $1,103]. (interquartile range (IQR) ¥ 0 – ¥449,378 [£3,043, €3,609, $4,130] and 2 (IQR 0–7), respectively.

Of the 1,080 individuals, 763 (70.6%) received at least one payment. Furthermore, 142 (13.1%) received payments totaling ≥¥1 million, while 19 (1.8%) received ≥¥5 million [£33,900, €40,200, $46,000]. Two individuals (0.2%) received ≥¥10 million [£67,700, €80,300, $91,900].

Respirology was the specialty which attracted the largest payment (¥216,806,522 [£1,467,884, €1,741,418, $1,992,707] from the pharmaceutical companies, followed by gastroenterology (¥139,690,202 [£945,770, €1,122,010, $1,283,917.00] and hematology (¥119,219,713 [£807,175, €957,588, $1,095,769].

Table 2 summarizes the monetary values and counts of payments made by the 78 pharmaceutical companies. In total, 59 (75.6%) companies made at least one payment to oncology specialists. The Chugai Pharmaceutical Co. Ltd., a subsidiary of F. Hoffmann-La Roche Ltd, made the largest accumulated payment of ¥103,830,493 [£702,982, € 833,980, $954,324]. The median monetary value and count among the 78 companies

was ¥645,946 [£4,373, €5,188, $5,937] (IQR ¥33,410 [£226, €268, $307] – ¥5,196,201 [£35,181, €41,737, $47,759] and 10 (IQR 1 – 71), respectively.

Table 3 ranks the oncology specialists according to the monetary value of the payments they received. In the HPG (N=142), females accounted for only 6.3% (9) of the total, while in the LPG (N=621), females accounted for 10.6% (66) of the total. However, females accounted for 30.9% (99) in the NPG (N=317). With respect to male recipients, 75.9% (688/907) received at least one payment, compared to only 43.4% of females (75/173). Of the oncologists in the HPG, 52.8% (75) worked for university hospitals and 28.2% (40) worked for cancer hospitals: these figures were higher than those seen in the other two groups. Further, while only 19.7% (28) of the specialists in the HPG were certified during the previous five years (2012 to 2016), 49.4% (307) and 60.3% (191) of individuals in the LPG and NPG respectively were certified during these five years. The proportion of specialist respirology oncologists was larger in the HPG (55, 38.7%) than in either the LPG (165, 26.6%) or NPG (65, 20.5%).

In the HPG, the total monetary value paid and number of payments were ¥418,345,258 [£2,832,398, €3,360,203, $3,845,085] and 4,466, respectively, accounting for 71.5% and 61.0% of the totals.

Table 4 displays findings of the multivariate regression analyses for the monetary value of payments. Female oncologists tended to receive a smaller value of payments than their male counterparts (relative monetary value [RMV] 0.40, 95% CI 0.20 – 0.79). Oncologists working for university hospitals (RMV 5.78, 95% CI 3.34 – 10.02) and those working for cancer hospitals (RMV 5.47, 95% CI 3.30 – 9.06) also tended to receive higher payments. Oncologists with longer experience after board certification were significantly more likely to receive larger payments compared with those with shorter experience (RMV 1.40, 95% CI 1.30 – 1.50). Those working in hematology were likely to receive smaller payments than those working in respirology (RMV 0.49, 95% CI 0.30 – 0.83). In the LPG and NPG, there were no significant differences in the monetary value of the payments with respect to the type of affiliation of recipients.

Figure 1 displays payment distributions to each cancer specialty on an individual company basis. Details of the payments are provided in Supplementary Material 2.

Further, in Supplementary Material 3, we summarize the list of high revenue generating oncology drugs. Chugai Pharmaceutical Co., Ltd. made the largest specialty payment of ¥ 103,830,493 [£702,982, €833,980, $954,324] and the top four specialties were gastroenterology (¥34,760,717 [£235,347, €279,203, $319,492], 33.5%), respirology (¥32,937,605 [£223,003, €264,559, $302,735], 31.7%), hematology (¥17,702,450 [£119,854, € 142,188, $162,706], 17.0%), and breast cancer (¥10,548,519 [£71,419, € 84,727, $96,953], 12.0%). The Chugai company manufactured eight high revenue generating oncology drugs (Supplementary Material 3), and four, three, one, and five drugs were respectively covered under the National Health Insurance scheme for the field of gastroenterology, respirology, hematology and breast cancer. Nivolumab (Opdivo®), manufactured by the Ono Pharmaceutical Co., Ltd., mainly used in lung cancer and melanoma, had the largest domestic sales in 2016 (¥103.9 billion [£703.5 million, €834.5 million, $955.0 million]). The total monetary value of the company's payments was ¥47,831,737 [£323,844, €384,191, $439,630], (representing fourth place in the payment table), of which ¥29,657,836 [£200,798, €238,216, $272,590] (62.0%) was specifically distributed to respirology specialists. All of the top eight companies with regard to the monetary value of the payments (Supplementary Material 2) had at least one drug which was newly approved or that had an added anticancer indication

under the National Health Insurance scheme in the fiscal years of 2015 and 2016 (Supplementary Material 4). While AstraZeneca Plc. had no high revenue generating oncology drugs (Supplementary Material 3), vandetanib (Caprelsa®) and osimertinib (Tagrisso®) were newly approved for thyroid cancer in September, 2015 and non-small cell lung cancer in March, 2016, respectively (Supplementary Material 4). The total monetary value of the company's payments was second, accounting for ¥51,928,785 [£351,583, €417,099, $477,287]. Of the total, 84.8% (¥44,013,864 [£297,995, €353,525, $404,539]) was specifically allocated to oncologists with a specialism in respirology.

The JSMO has established a guideline on COI disclosure for its members which requires them to disclose any COI associated with publications and other research presentations. Further, Executive Board members, auditors, and other high-level members, as well as Presidents and Vice-Presidents of conferences and committee members operating under the JSMO are required to disclose any COI associated with their work and positions. These include, with respect to any for-profit organization, reporting any 1) position as an officer or advisor, 2) stock ownership, 3) patent royalties or licensing fees, 4) honoraria (e.g. lecture fees), 5) fees paid for any writing or publication work, 6) receipt of research funding, 7) advisory fees or financial

remuneration in exchange for testimony, 8) acceptance of researchers from any for-profit enterprise, 9) endowed chairs offered, and 10) any remuneration (travel, gifts, or other in-kind payments not directly related to research). However, there are no rules specifically referring to oncology specialists.

Discussion

In 2016, approximately ¥600 million [£4.1 million, €4.8 million, $5.5 million] was paid by Japanese pharmaceutical companies to 763 (70.6%) certified oncology specialists. Payments appeared to be concentrated on specific targets, notably experienced male oncologists working for university hospitals and cancer hospitals.

The proportion of oncologists receiving payments was larger compared with general physicians in the US (48.0%)[30] and Japan (33.3%).[31] However, the proportion was slightly smaller than that of NCCN oncology CPG authors in the US (86.4%).[19] Although the mean value of payments in our study was approximately half of that of the CPG authors ($4,982 [data not shown] vs.$10,011), a simple comparison is not valid, as our analysis only covered data for speaking, writing and consultancy work. It did not include payments related to meals, transportation and accommodation, stock ownership,

investment interest, or payments from medical device companies, as is complied in the US's Open Payments database.[30] The CPG authors strongly influence oncology practice, both in the US and internationally,[32] by recommending treatment algorithms. They may well be identified as prime targets for representatives of Pharma attempting to promote the sale of their anticancer products. It is thus reasonable to assume that Japanese Pharma with similar anticancer interests may well be trying to target oncology specialists in an attempt to help boost the sales and use of their specific products.

We observed a large disparity in payments to specialists. Those receiving ¥1 million or more accounted for 13.1% of all oncologists studied but received 71.5% of the total paid. Oncologists working for university hospitals and those working for cancer hospitals similarly received large value payments. In Japan, cancer centers are generally more likely to treat more cancer patients compared to university hospitals. Indeed, cancer centers top the nationwide ratings for treatments of most of the common cancers, including lung, colon, gastric, and breast cancer.[33] In contrast, university hospitals are regarded as symbols of academic excellence and authority, and medical school professors traditionally have a strong influence on both physicians and medical practice in their field of expertise. They are more influential in setting treatment protocols which

are usually followed without question by less senior medical staff nationwide. Thus, our findings suggest that Japanese pharmaceutical companies have placed emphasis on expertise and authority, as well as clinical experience, in the selection of targets for their promotional activities.

A particularly significant finding was that a smaller proportion of female oncologists received payments from Pharma compared to their male colleagues. Furthermore, women also tended to receive smaller payment amounts than men. These findings are in line with similar studies performed in the US.[34 35] In the relatively unique, patriarchal Japanese society, there may be very specific reasons for these results. Firstly, there are far fewer female oncologists than males and they have considerably less spare time for industry-related work due to women needing to fulfill their socially-perceived duty to be the main person responsible for raising any children in the family.[36] Further, Pharma may tend to target men rather than women[34] because in Japan's male-dominated society, the status of women has traditionally been low, and their contribution, presence and influence in biomedicine and the higher echelons of power and influence has not been actively encouraged.[37 38]

We found that respirology attracted the greatest financial outlay. In Japan, lung cancer is of primary concern at present, covering a large patient volume and consequently attracting multiple novel oncology drugs, such as alectinib (Alecensa®) (Chugai Pharmaceutical Co., Ltd., [approved 2014]), nivolumab (Opdivo®) (Ono Pharmaceutical Co., Ltd, [approved 2015]), afatinib (Gilotrif®) (Nippon Boehringer lngelheim Co., Ltd., [approved 2016]), ceritinib (Zykadia®) (Novartis Pharma K.K., [approved 2016]), osimertinib (Tagrisso®) (AstraZeneca plc, [approved 2016]), pembrolizumab (Keytruda®) (MSD K.K., [approved 2016]), ramucirumab (Cyramza®) (Eli Lilly Japan K.K., [approved 2016]), all for non-small cell lung cancer (Supplementary Materials 3 & 4). As such, for the pharmaceutical companies, this field is a critical yet highly competitive target in any strategy to maximize the cost-effectiveness of their promotional endeavors.

The examples of Chugai Pharmaceutical and Ono Pharmaceutical chiefly support the belief that there is an association between the value and destination of payments dependent on the products the companies in question manufacture. In contrast, the example of AstraZeneca adds credence to the notion that that funds were mainly allocated to promote their novel product: osimertinib (Tagrisso®) was approved for

non-small cell lung cancer in March 2016. Indeed, 84.8% of the company's total payment was allocated to respirology specialists.

As we have demonstrated, there are extensive financial relationships between pharmaceutical companies and oncologists in Japan. It is true that the receipt of payments by physicians in Japan is not illegal, especially as they are supposedly given as remuneration for work undertaken or services rendered. However, we believe that there is an ethical problem inherent in such relationships, given that this practice can be seen by the public and neutral observers as being instigated and developed to possibly end up expanding the profit of pharmaceutical companies, rather than promoting the health and well-being of patients. Indeed, even a subtle but reputable financial relationship with the industry, such as collaborating in a field trial, could bias a physician's prescription patterns in a manner that benefits the companies.[13-18] Oncologists handle extraordinary and very potent life-saving drugs, and have a degree of autonomy in their prescribing actions. Their decisions substantially influence the treatment and outcome for their patients, as well as having significant economic impact due to the high cost of anticancer medications.[5-7] It would therefore appear sensible to have regulations in place which necessitate the open and accessible reporting of any

financial dealings between physicians and Pharma, so as to avoid any potential nefarious or underhand behavior or undue pressure on physicians to alter their usual treatment practices. Indeed, it is possible that these arrangements may have contributed to the multiple cases of scientific misconduct that have recently been reported in Japan. The most infamous case was when employee misconduct was discovered in a series of clinical trials for Valsartan, an antihypertensive medication manufactured by Novartis Pharma KK, leading to a retraction of the associated academic papers.[39 40] Also, the company illegally (or unethically) obtained the information about patients participating in another clinical trial for chronic myelogenous leukemia using nilotinib (Tasigna®) from a university hospital in Japan.[41 42] A breast cancer clinical trial (CREATE-X trial) with a questionable pharmaceutical payment has also been identified.[43 44]

Since January, the new regulations in Japan have already been weakened by allowing Pharma to aggregate payment data they should publish into a single amount, making matters much less transparent.[45] To prevent similar cases in future, we call for the implementation of a transparent, independent mechanism that would enable a comprehensive assessment of any and all payments being made by any pharmaceutical company to any individual physician or, for that matter, medical institution where the

company's products may be used - and not just with respect to oncology. Ideally, these actions should be mandatory and legally-binding on the side of both the company and physician. New schemes along these lines, such as the US's Open Payments Database, may prove successful but it is too soon to know.[46] The Disclosure UK mechanism may not prove to be so effective as it is voluntary.[47] Additionally, given that such mechanisms allow for direct comparison between what is allegedly paid and what is allegedly received, any new system will probably necessitate a fair, equitable and timely mechanism for dispute settlement, probably involving the use of third parties.[44]

Study Limitations

Several limitations in this preliminary study should be acknowledged. First, there could be measurement errors in the affiliations and subspecialties of the included specialists, as we collated these data in the study year (2016), using the websites and other data sources on the Internet. Second, there might be minor measurement errors in the payment database as well. Most of the pharmaceutical companies involved did not disclose their payment data in a uniform or readily available format. As a result, we manually entered all the payment data from a variety of formats, and, despite repeated and careful review, the database may include minor errors. Third, the present research

analyzed only limited payment types, namely speaking, writing and consultancy work. Currently, Japanese pharmaceutical companies do not disclose any payment data for stock holdings, royalties, individual data for costs of meals, transportation and accommodation, etc. As, unlike the pharmaceutical companies, the JMSO and other similar academic and learned societies in Japan, where such data may be registered, refuse to open their databases on payments to public scrutiny, we were not able to consider these data in this study. Fourth, most of the pharmaceutical companies only publish single year data so we could only consider payments made in fiscal 2016. To understand temporal trends and the extent and distribution of pharmaceutical company payments, a continuous assessment of the payment data is warranted in future.

Concluding remarks

Japanese certified oncologists receive financial payments directly from pharmaceutical companies, usually from companies active in the specialist field of the physician in question. In today's prevailing climate of Fake News, inaccurate scientific data, Vaccine Hesitancy, and suspicion about many financial dealings involving Pharma, this raises several queries with regard to ethical, medical, and legal issues. The value and specialty targets of the payments varied substantially, which also raises yet more

questions as to why. We believe that the lessons learned from our analyses should be shared among the global medical community to help put in place safeguards to prevent any form of inducements from the pharmaceutical industry and to help protect physicians from outside influences. It is essential to establish a robust, comprehensive and legally-binding system for identifying and avoiding any and all potential COIs, of any nature, involving physicians or other medical professionals, both in Japan and internationally. While it is too early to evaluate whether similar systems, such as the US-based Open Payments Database, will be truly effective, financial transparency is a fundamental component in illustrating that there is an open, honest and ethically correct relationship between pharmaceutical companies and physicians. A more comprehensive study is planned, to include all Japanese oncologists, to try and confirm our findings and to help identify the best way forward to ensure that COIs are minimized and so that physicians and pharmaceutical companies can work harmoniously and synergistically to provide Japan with the best cancer prophylaxis, treatment and cures possible.

Ethics approval

This study was approved by the Institutional Review Board of the Medical Governance Research Institute (MEGRI) on 16th May 2018.

Author contributors

AO acquired and controlled all sources of data, and oversaw all data analyses.

AO, HS, YO, TS, YShim, YSom, AT, and TT were involved in the study concept and design.

AO, HS, YO, TS, YShim, YSom, AT, and TT were involved in the analysis, interpretation of results and formation of conclusions.

A.O. drafted the manuscript.

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Role of funding source

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Conflict of Interest statement

AO and TT receive personal fees from Medical Network Systems (MNES Inc.); HS has received a research honorarium from TAIHO Pharmaceutical Co., Ltd. All other authors declare no conflict of interests.

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Data availability statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band color represents the payment destination specialties. Due to space limitations, names of companies with payment values of less than ¥10 million (£67,700, €80,300, $91,900) have been omitted.

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744 **Table 1. Characteristics of oncology specialists and pharmaceutical payment**

745 **received by individual doctors.**

Variable	
1. Characteristics of oncology specialists (N=1080)	
Sex (N, %)	
Men	907 (84.0)
Women	173 (16.0)
Working institutions (N, %)	
University hospitals	442 (40.9)
Cancer hospitals	183 (16.9)
Other types of institutions	455 (42.1)
Working regions (N, %)	
Hokkaido	52 (4.8)
Tohoku	58 (5.4)
Kanto	302 (28.0)
Chubu	194 (18.0)
Kinki	208 (19.3)
Chugoku	88 (8.2)
Shikoku	43 (4.0)
Kyushu	135 (12.5)
Year of certification (N, %)	
2006	45 (4.2)
2007	77 (7.1)
2008	71 (6.6)
2009	98 (9.1)
2010	133 (12.3)
2011	130 (12.0)
2012	124 (11.5)
2013	143 (13.2)
2014	98 (9.1)
2015	85 (7.9)
2016	76 (7.0)
Specialty (N, %)	
Respirology	285 (26.4)
Gastroenterology	278 (25.7)
Hematology	250 (23.2)
Breast	72 (6.7)
Head and neck	12 (1.1)
Gynaecology	10 (0.9)
Urology	9 (0.8)
Dermatology	2 (0.2)
Other or undetermined	162 (15.0)

2. Characteristics of payment (N=1080)	
Total monetary value of payment	585,453,314 [3,963,800]
Total count of payment	7,325
Type of payment (¥ [£], %)	
Speaking	467,802,690 [3,167,249], 79.9
Consulting	94,682,807 [641,048], 16.2
Writing	22,266,186 [150,753], 3.8
Missing	701,631 [4,750], 0.1
Payment per individual specialist	
Median value per individual specialist (¥ [£], Interquartile range)	120,016 [813] (0 [0] – 449,378 [3,043])
Median count per individual specialist (Interquartile rage)	2 (0–7)
Number of oncology specialists with payment (N, %)	
Any	763 (70.6)
¥1 million [£6,800] or above	142 (13.1)
¥5 million [£33,900] or above	19 (1.8)
¥10 million [£67,700] or above	2 (0.2)
Monetary value of payment according to specialties (¥ [£], %)	
Respirology	216,806,522 [1,467,884], 37.0
Gastroenterology	139,690,202 [945,770], 23.9
Hematology	119,219,713 [807,175], 20.4
Breast	49,287,661 [333,701], 8.4
Head and neck	9,213,401 [62,379], 1.6
Gynaecology	570,533 [3,863], 0.1
Urology	7,862,285 [53,231], 1.3
Dermatology	562,502 [3,808], 0.1
Other or undetermined	42,240,495 [285,988], 7.2

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

Table 2. Companies making a payment to oncology specialists and monetary value and count of their payment

Pharmaceutical company	Monetary value (¥ [£])	Count
Chugai Pharmaceutical Co., Ltd.	103,830,493 [702,982]	1,248
AstraZeneca plc	51,928,785 [351,583]	592
Taiho Pharmaceutical Co., Ltd.	50,723,560 [343,423]	688
Ono Pharmaceutical Co., Ltd.	47,831,737 [323,844]	624
Eli Lilly Japan K.K.	44,825,340 [303,489]	502
Bristol-Myers Squibb K.K.	33,443,966 [226,432]	405
Takeda Pharmaceutical Company Ltd.	28,280,960 [191,476]	306
Novartis Pharma K.K.	27,203,346 [184,180]	336
Nippon Boehringer Ingelheim Co., Ltd.	25,987,859 [175,950]	325
Kyowa Hakko Kirin Company, Ltd.	20,208,095 [136,819]	267
Pfizer Japan Inc.	16,509,478 [111,777]	185
Merck Serono Co., Ltd.	16,377,746 [110,885]	229
Eisai Co., Ltd.	16,309,136 [110,421]	220
Celgene Corporation	15,207,296 [102,961]	212
Daiichi Sankyo Company, Limited.	8,772,101 [59,391]	117
Bayer Yakuhin, Ltd.	8,340,481 [56,469]	97
Yakult Honsha Company, Limited.	8,318,026 [56,317]	121
Janssen Pharmaceutical K.K.	7,723,516 [52,292]	84
MSD K.K.	6,317,468 [42,772]	71
Sumitomo Dainippon Pharma Co., Ltd.	5,196,201 [35,181]	92
Nippon Kayaku Co., Ltd.	3,868,780 [26,194]	46
Astellas Pharma Inc.	3,590,000 [24,306]	53
Nippon Shinyaku Co., Ltd.	3,129,497 [21,188]	53
Asahi Kasei Pharma Corporation	3,102,452 [21,005]	45
Sanofi K.K.	2,592,500 [17,552]	31
Otsuka Holdings Co., Ltd.	2,204,198 [14,923]	40
Mochida Pharmaceutical Co., Ltd.	2,149,441 [14,553]	31
Teijin Pharma Limited.	2,099,790 [14,217]	27
AbbVie GK,	2,082,626 [14,100]	17
Shionogi & Co., Ltd.	1,948,968 [13,195]	28
Kyorin Pharmaceutical Co., Ltd.	1,918,033 [12,986]	34
Tsumura & Co.	1,681,688 [11,386]	21
Meiji Seika Pharma Co., Ltd.	1,289,000 [8,727]	24
Terumo Corporation	1,214,840 [8,225]	16
Kissei Pharmaceutical Co., Ltd.	1,124,840 [7,616]	9
Zeria Pharmaceutical Co., Ltd.	946,645 [6,409]	12
Mitsubishi Tanabe Pharma Corporation	935,508 [6,334]	17
EA Pharma Co., Ltd.	783,712 [5,306]	17
Taisho Toyama Pharmaceutical Co., Ltd.	701,631 [4,750]	11
Kowa Company, Ltd.	590,262 [3,996]	5
Hisamitsu Pharmaceutical Co., Inc.	539,030 [3,649]	11

Novo Nordisk Pharma Ltd.	474,360 [3,212]	8
Sanwa Kagaku Kenkyusho Co., Ltd.	445,480 [3,016]	4
Aska Pharmaceutical Co., Ltd.	423,206 [2,865]	6
Shire Japan K.K	367,521 [2,488]	5
Nihon Pharmaceutical Co., Ltd.	311,836 [2,111]	8
Nippon Chemiphar Co., Ltd.	278,425 [1,885]	3
Ayumi Pharmaceutical Corporation	226,864 [1,536]	3
Mylan Seiyaku Ltd.	206,240 [1,396]	4
Kracie Holdings, Ltd.	134,056 [908]	2
GlaxoSmithKline K.K.	111,370 [754]	2
Minophagen Pharmaceutical Co.	110,440 [748]	2
Maruho Co., Ltd.	103,120 [698]	1
Torii Pharmaceutical Co., Ltd.	102,260 [692]	2
EN Otsuka Pharmaceutical Co., Ltd.	89,096 [603]	2
Kaken Pharmaceutical Co., Ltd.	77,959 [528]	1
Toray Industries, Inc.	77,080 [522]	1
Santen Pharmaceutical Co., Ltd.	51,560 [349]	1
Toyama Chemical Co., Ltd.	33,410 [226]	1
Bee Brand Medico Dental. Co., Ltd.	0 [0]	0
Biofermin Seiyaku Co., Ltd.	0 [0]	0
Fujimoto Pharmaceutical Corporation	0 [0]	0
Fuso Pharmaceutical Industries, Ltd.	0 [0]	0
Japan Tobacco Inc.	0 [0]	0
Kyoto Pharmaceutical Industries, Ltd.	0 [0]	0
Maruishi Pharmaceutical Co., Ltd.	0 [0]	0
Nippon Zoki Pharmaceutical Co., Ltd.	0 [0]	0
Otsuka Pharmaceutical Co., Ltd.	0 [0]	0
Otsuka Pharmaceutical Factory, Inc.	0 [0]	0
POLA-Pharma.	0 [0]	0
Research Institute for Microbial Diseases	0 [0]	0
Seikagaku Corporation	0 [0]	0
Senju Pharmaceutical Co., Ltd.	0 [0]	0
Taisho Pharmaceutical Co., Ltd.	0 [0]	0
Teikoku Seiyaku Co., Ltd.	0 [0]	0
Toa Eiyo Ltd.	0 [0]	0
UCB Japan Co., Ltd.	0 [0]	0
Wakamoto Pharmaceutical Co., Ltd.	0 [0]	0

751 We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly

752 exchange rate for 2016, namely ¥147.7 yen per £1.

753

Table 3. Characteristics of oncology specialists and pharmaceutical company payments received in 2016, according to the monetary value of the payment

Variable	High-payment Group (¥1 million [£6,800] or more) (N=142)	Low-payment Group (¥1 – 1 million [£6,800]) (N=621)	No-payment Group (¥0) (N=317)
Characteristics of oncology specialists			
Sex (N, %)			
Men	133 (93.7)	555 (89.4)	219 (69.1)
Women	9 (6.3)	66 (10.6)	98 (30.9)
Working institutions (N, %)			
University hospitals	75 (52.8)	248 (39.9)	119 (37.5)
Cancer hospitals	40 (28.2)	98 (15.8)	45 (14.2)
Other types of institutions	27 (19.0)	275 (44.3)	153 (48.3)
Working regions (N, %)			
Hokkaido	4 (2.8)	37 (6.0)	11 (3.5)
Tohoku	11 (7.8)	30 (4.8)	17 (5.4)
Kanto	45 (31.7)	162 (26.1)	95 (30.0)
Chubu	23 (16.2)	113 (18.2)	58 (18.3)
Kinki	29 (20.4)	108 (17.4)	71 (22.4)
Chugoku	9 (6.3)	60 (9.7)	19 (6.0)
Shikoku	5 (3.5)	31 (5.0)	7 (2.2)

Kyushu	16 (11.3)	80 (12.9)	39 (12.3)
Year of certification (N, %)			
2006	22 (15.5)	21 (3.4)	2 (0.6)
2007	15 (10.6)	46 (7.4)	16 (5.1)
2008	19 (13.4)	38 (6.1)	14 (4.4)
2009	19 (13.4)	56 (9.0)	23 (7.3)
2010	23 (16.2)	80 (12.9)	30 (9.5)
2011	16 (11.3)	73 (11.8)	41 (12.9)
2012	9 (6.3)	72 (11.6)	43 (13.6)
2013	9 (6.3)	79 (12.7)	55 (17.4)
2014	5 (3.5)	65 (10.5)	28 (8.8)
2015	2 (1.4)	51 (8.2)	32 (10.1)
2016	3 (2.1)	40 (6.4)	33 (10.4)

Specialty (N, %)			
Respirology	55 (38.7)	165 (26.6)	65 (20.5)
Gastroenterology	33 (23.2)	178 (28.7)	67 (21.1)
Hematology	28 (19.7)	139 (22.4)	83 (26.2)
Breast	16 (11.3)	34 (5.5)	22 (6.9)
Head and neck	3 (2.1)	4 (0.6)	5 (1.6)
Gynaecology	0 (0.0)	5 (0.8)	5 (1.6)
Urology	1 (0.7)	6 (1.0)	2 (0.6)
Dermatology	0 (0.0)	1 (0.2)	1 (0.3)
Other or undetermined	6 (4.2)	89 (14.3)	67 (21.1)
Characteristics of pharmaceutical payment			
Total payment			
Total value of payment (¥ [£])	418,345,258 [2,832,398]	167,108,056 [1,131,402]	
Total count of payment	4,466	2,859	
Type of payment (¥ [£], %)			
Speaking	327,075,925 [2,214,461], 78.2	140,726,765 [952,788], 84.2	
Consulting	73,870,218 [500,137], 17.7	20,812,589 [140,911], 12.5	
Writing	17,053,868 [115,463], 4.1	5,212,318 [35,290], 3.1	
Missing	345,247 [2,337], 0.1	356,384 [2,413], 0.2	
Payment per individual specialist			
Median monetary value (¥ [£],	2,269,622 [15,366] (1,439,448 [9,746] – 3,681,775	171,086 [1,158] (89,096 [603] – 380,886	

Interquartile range)	[24,927])	[2,579])
Median count (Interquartile range)	24 (19 – 38)	3 (2 – 6)
Monetary value of payment according to specialties (¥ [£], %)		
Respirology	169,761,707 [1,149,368], 40.6	47,044,815 [318,516], 28.2
Gastroenterology	92,334,612 [625,150], 22.1	47,335,590 [320,485], 28.3
Hematology	81,963,421 [554,932], 19.6	37,256,292 [252,243], 22.3
Breast	42,090,455 [284,973], 10.1	7,197,206 [48,729], 4.3
Head and neck	8,689,962 [58,835], 2.1	523,439 [3,544], 0.3
Gynaecology	0 [0], 0	570,533 [3,863], 0.3
Urology	5,527,458 [37,424], 1.3	2,334,827 [15,808], 1.4
Dermatology	0 [0], 0	562,502 [3,808], 0.3
Other or undetermined	17,977,643 [121,717], 4.3	24,262,852 [164,271], 14.5

757 We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

Table 4. Multivariate negative binomial model for the monetary value of payment on an individual basis

Variable	All (N=1080) Relative monetary value per year (95% CI)	Low-payment and No-payment Groups (¥0 – 1 million [£6,800]) (N=938) Relative monetary value per year (95% CI)
Sex		
Men	Ref.	Ref.
Women	0.40 (0.20 – 0.79)***	0.40 (0.28 – 0.58)***
Types of affiliations		
Other type of institutions	Ref.	Ref.
University hospitals	5.78 (3.34 – 10.02)***	1.08 (0.80 – 1.47)
Cancer hospitals	5.47 (3.30 – 9.06)***	1.11 (0.90 – 1.37)
Working region		
Kanto	Ref.	Ref.
Hokkaido	0.45 (0.16 – 1.26)	0.82 (0.54 – 1.23)
Tohoku	1.41 (0.62 – 3.20)	1.07 (0.69 – 1.67)
Chubu	0.86 (0.41 – 1.81)	0.96 (0.72 – 1.29)
Kinki	1.14 (0.66 – 1.96)	0.74 (0.54 – 1.03)

Chugoku	1.47 (0.50 – 4.32)	0.80 (0.53 – 1.22)
Shikoku	0.69 (0.32 – 1.53)	1.22 (0.78 – 1.89)
Kyushu	1.18 (0.55 – 2.51)	1.04 (0.74 – 1.45)
Year of experience after the board certification	1.40 (1.30 – 1.50)***	1.13 (1.09 –1.17)***
Subspecialty		
Respirology	Ref.	Ref.
Gastroenterology	0.57 (0.32 – 1.01)	0.94 (0.72 – 1.22)
Hematology	0.49 (0.30 – 0.83)**	0.76 (0.57 – 1.00)*
Breast	1.50 (0.68 – 3.33)	0.73 (0.45 – 1.19)
Other or undetermined†	0.28 (0.12 – 0.64)**	0.69 (0.51 – 0.93)*

† Other or undetermined specialties included Head and neck cancer, Gynaecology, Urology and Dermatology. Due to the small number of physicians in these four specialties, they were included in the "other or undetermined" category; CI=Confidence interval; * <0.05, ** <0.01, *** <0.001

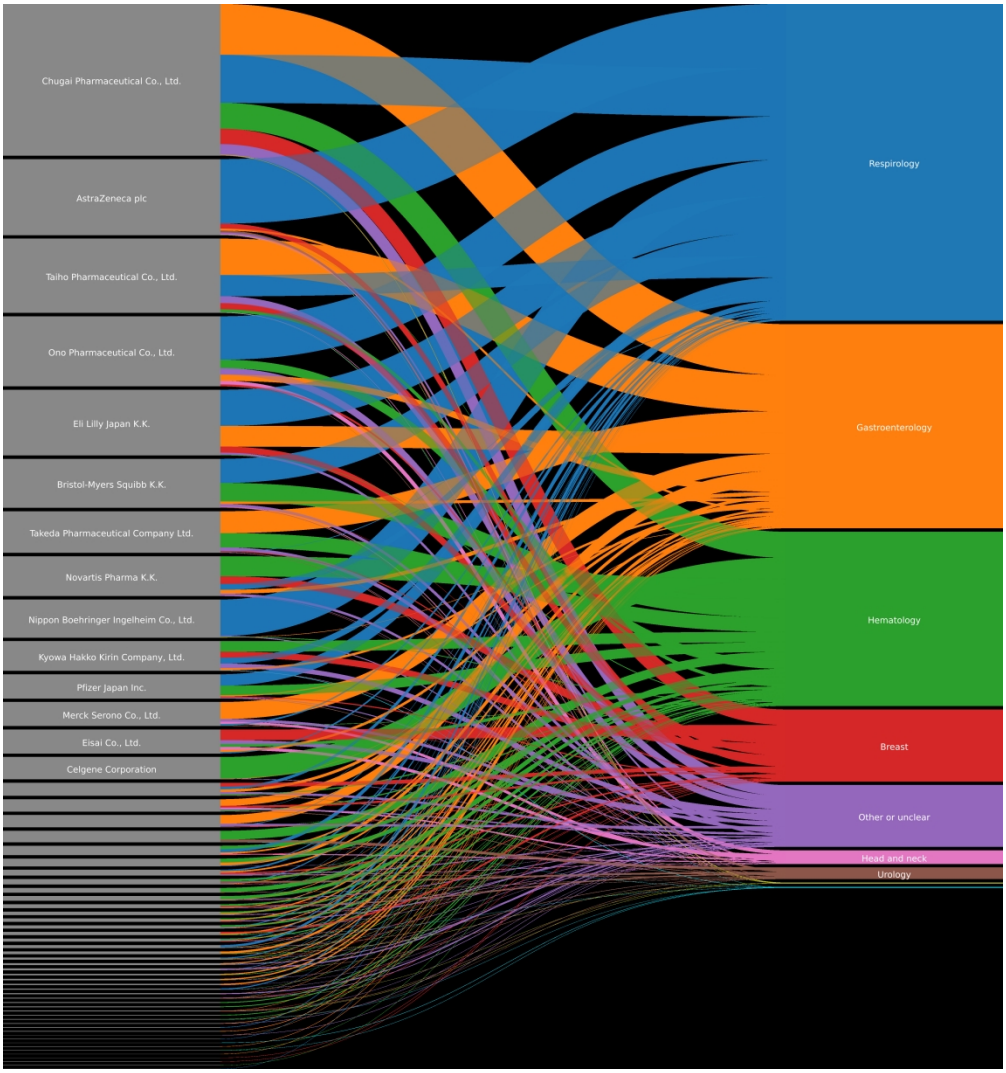

Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band color represents the payment destination specialties. Due to space limitations, names of companies with payment values of less than ¥10 million (£67,700, €80,300, $91,900) have been omitted.

Supplementary Material 1. Seventy-eight pharmaceutical companies sampled and the start and end date of the period when the payment data was disclosed

Pharmaceutical company	Period of the payment data in 2016	
	Start date	End date
AbbVie GK	January 1, 2016	December 31, 2016
Asahi Kasei Pharma Corporation	April 1, 2016	March 31, 2017
Aska Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Astellas Pharma Inc.	April 1, 2016	March 31, 2017
AstraZeneca plc	January 1, 2016	December 31, 2016
Ayumi Pharmaceutical Corporation	April 1, 2016	March 31, 2017
Bayer Yakuhin, Ltd.	January 1, 2016	December 31, 2016
Bee Brand Medico Dental. Co., Ltd.[a]	April 1, 2016	March 31, 2017
Biofermin Seiyaku Co., Ltd.[b]	April 1, 2016	March 31, 2017
Bristol-Myers Squibb K.K.	April 1, 2016	March 31, 2017
Celgene Corporation	January 1, 2016	December 31, 2016
Chugai Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Daiichi Sankyo Company, Limited.	April 1, 2016	March 31, 2017
EA Pharma Co., Ltd.	April 1, 2016	March 31, 2017
Eisai Co., Ltd.	January 1, 2016	December 31, 2016
Eli Lilly Japan K.K.	January 1, 2016	December 31, 2016
EN Otsuka Pharmaceutical Co., Ltd.[c]	January 1, 2016	December 31, 2016
Fujimoto Pharmaceutical Corporation	July 1, 2016	June 30, 2017
Fuso Pharmaceutical Industries, Ltd.	April 1, 2016	March 31, 2017
GlaxoSmithKline K.K.	January 1, 2016	December 31, 2016
Hisamitsu Pharmaceutical Co., Inc.	March 1, 2016	February 28, 2017
Janssen Pharmaceutical K.K.	January 1, 2016	December 31, 2016
Japan Tobacco Inc.[d]	Not available	Not available
Kaken Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Kissei Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Kowa Company, Ltd.	April 1, 2016	March 31, 2017
Kracie Holdings, Ltd.	January 1, 2016	December 31, 2016
Kyorin Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017

Kyoto Pharmaceutical Industries, Ltd.	June 1, 2016	May 31, 2017
Kyowa Hakko Kirin Company, Ltd.	January 1, 2016	December 31, 2016
Maruho Co., Ltd.	October 1, 2016	September 30, 2017
Maruishi Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Meiji Seika Pharma Co., Ltd.	April 1, 2016	March 31, 2017
Merck Serono Co., Ltd.	January 1, 2016	December 31, 2016
Minophagen Pharmaceutical Co.	April 1, 2016	March 31, 2017
Mitsubishi Tanabe Pharma Corporation	April 1, 2016	March 31, 2017
Mochida Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
MSD K.K.	January 1, 2016	December 31, 2016
Mylan Seiyaku Ltd.	January 1, 2016	December 31, 2016
Nihon Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Nippon Boehringer Ingelheim Co., Ltd.	January 1, 2016	December 31, 2016
Nippon Chemiphar Co., Ltd.	January 1, 2016	December 31, 2016
Nippon Kayaku Co., Ltd.	April 1, 2016	March 31, 2017
Nippon Shinyaku Co., Ltd.	April 1, 2016	March 31, 2017
Nippon Zoki Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Novartis Pharma K.K.	January 1, 2016	December 31, 2016
Novo Nordisk Pharma Ltd.	January 1, 2016	December 31, 2016
Ono Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Otsuka Holdings Co., Ltd.[e]	January 1, 2016	December 31, 2016
Otsuka Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Otsuka Pharmaceutical Factory, Inc.[f]	January 1, 2016	December 31, 2016
Pfizer Japan Inc.	December 1, 2015	November 30, 2016
POLA-Pharma.	January 1, 2016	December 31, 2016
Research Institute for Microbial Diseases	April 1, 2016	March 31, 2017
Sanofi K.K.	January 1, 2016	December 31, 2016
Santen Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Sanwa Kagaku Kenkyusho Co., Ltd.	April 1, 2016	March 31, 2017
Seikagaku Corporation	April 1, 2016	March 31, 2017
Senju Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Shionogi & Co., Ltd.	April 1, 2016	March 31, 2017
Shire Japan K.K.	January 1, 2016	December 31, 2016
Sumitomo Dainippon Pharma Co., Ltd.	April 1, 2016	March 31, 2017

Taiho Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Taisho Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Taisho Toyama Pharmaceutical Co., Ltd.[g]	April 1, 2016	March 31, 2017
Takeda Pharmaceutical Company Ltd.	April 1, 2016	March 31, 2017
Teijin Pharma Limited.	April 1, 2016	March 31, 2017
Teikoku Seiyaku Co., Ltd.	January 1, 2016	December 31, 2016
Terumo Corporation	April 1, 2016	March 31, 2017
Toa Eiyo Ltd.	April 1, 2016	March 31, 2017
Toray Industries, Inc.	April 1, 2016	March 31, 2017
Torii Pharmaceutical Co., Ltd.	January 1, 2016	December 31, 2016
Toyama Chemical Co., Ltd.	April 1, 2016	March 31, 2017
Tsumura & Co.	April 1, 2016	March 31, 2017
UCB Japan Co., Ltd.	January 1, 2016	December 31, 2016
Wakamoto Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
Yakult Honsha Company, Limited.	April 1, 2016	March 31, 2017
Zeria Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017

[a] Affiliated company of Ono Pharmaceutical Co., Ltd.; [b] affiliated company of Taisho Pharmaceutical Co., Ltd.; [c] affiliated company of Otsuka Pharmaceutical Co., Ltd.; [d] the company left the Japan Pharmaceutical Manufacturers Association on March 31, 2018; [e] affiliated company of Otsuka Pharmaceutical Co., Ltd.; [f] affiliated company of Otsuka Pharmaceutical Co., Ltd.; [g] affiliated company of Taisho Pharmaceutical Co., Ltd. and Toyama Chemical Co., Ltd.

Supplementary Material 2. Monetary value of payment (¥ [£]) in each company according to oncology subspecialty

Company	Respirology	Gastroenterology	Hematology	Breast	Head and neck	Gynaecology	Urology	Dermatology	Other or unclear	Total
Chugai Pharmaceutical Co., Ltd.	32,937,605 [223,003]	34,760,717 [235,347]	17,702,450 [119,854]	10,548,519 [71,419]	0 [0]	332,202 [2,249]	229,104 [1,551]	0 [0]	7,319,896 [49,559]	103,830,493 [702,982]
AstraZeneca plc	44,013,864 [297,995]	1,342,002 [9,086]	111,370 [754]	3,454,557 [23,389]	623,673 [4,223]	77,959 [528]	1,269,618 [8,596]	0 [0]	1,035,742 [7,012]	51,928,785 [351,583]
Taiho Pharmaceutical Co., Ltd.	14,561,511 [98,588]	24,880,266 [168,451]	2,116,030 [14,327]	4,176,377 [28,276]	222,740 [1,508]	33,411 [226]	0 [0]	33,411 [226]	4,699,814 [31,820]	50,723,560 [343,423]
Ono Pharmaceutical Co., Ltd.	29,657,836 [200,798]	4,219,238 [28,566]	5,746,692 [38,908]	1,124,838 [7,616]	2,450,141 [16,589]	0 [0]	133,644 [905]	0 [0]	4,499,348 [30,463]	47,831,737 [323,844]
Eli Lilly Japan K.K.	24,707,436 [167,281]	14,101,874 [95,476]	412,069 [2,790]	4,145,014 [28,064]	0 [0]	0 [0]	0 [0]	0 [0]	1,458,947 [9,878]	44,825,340 [303,489]
Bristol-Myers Squibb K.K.	16,471,626 [111,521]	1,848,742 [12,517]	12,617,772 [85,428]	33,411 [226]	356,384 [2,413]	0 [0]	334,111 [2,262]	0 [0]	1,781,920 [12,064]	33,443,966 [226,432]
Takeda Pharmaceutical Company Ltd.	329,974 [2,234]	14,889,129 [100,807]	9,781,123 [66,223]	579,124 [3,921]	57,276 [388]	0 [0]	286,381 [1,939]	0 [0]	2,357,953 [15,964]	28,280,960 [191,476]
Novartis Pharma K.K.	4,031,596 [27,296]	2,609,889 [17,670]	13,667,153 [92,533]	5,260,980 [35,619]	77,959 [528]	0 [0]	55,685 [377]	0 [0]	1,500,084 [10,156]	27,203,346 [184,180]
Nippon Boehringer Ingelheim Co., Ltd.	24,840,981 [168,185]	189,329 [1,282]	434,110 [2,939]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	523,439 [3,544]	25,987,859 [175,950]

Kyowa Hakko Kirin Company, Ltd.	4,065,005 [27,522]	1,425,536 [9,652]	7,127,681 [48,258]	4,181,946 [28,314]	111,370 [754]	0 [0]	0 [0]	222,740 [1,508]	3,073,817 [20,811]	20,208,095 [136,819]
Pfizer Japan Inc.	7,782,876 [52,694]	788,768 [5,340]	6,543,478 [44,302]	638,311 [4,322]	0 [0]	0 [0]	217,649 [1,474]	0 [0]	538,396 [3,645]	16,509,478 [111,777]
Merck Serono Co., Ltd.	1,002,330 [6,786]	11,588,836 [78,462]	245,014 [1,659]	111,370 [754]	1,603,728 [10,858]	0 [0]	0 [0]	0 [0]	1,826,468 [12,366]	16,377,746 [110,885]
Eisai Co., Ltd.	890,961 [6,032]	1,624,796 [11,001]	1,982,386 [13,422]	7,244,821 [49,051]	1,948,977 [13,196]	0 [0]	0 [0]	0 [0]	2,617,195 [17,720]	16,309,136 [110,421]
Celgene Corporation	0 [0]	226,864 [1,536]	14,722,632 [99,679]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	257,800 [1,745]	15,207,296 [102,961]
Daiichi Sankyo Company, Limited.	1,826,473 [12,366]	1,789,335 [12,115]	700,236 [4,741]	2,615,204 [17,706]	0 [0]	0 [0]	389,796 [2,639]	0 [0]	1,451,057 [9,824]	8,772,101 [59,391]
Bayer Yakuhin, Ltd.	77,959 [528]	4,397,978 [29,776]	645,946 [4,373]	1,264,054 [8,558]	863,118 [5,844]	0 [0]	278,425 [1,885]	0 [0]	813,001 [5,504]	8,340,481 [56,469]
Yakult Honsha Company, Limited.	412,486 [2,793]	5,946,230 [40,259]	51,561 [349]	381,548 [2,583]	0 [0]	0 [0]	0 [0]	0 [0]	1,526,201 [10,333]	8,318,026 [56,317]
Janssen Pharmaceutical K.K.	0 [0]	0 [0]	5,924,886 [40,114]	0 [0]	0 [0]	0 [0]	1,742,945 [11,801]	55,685 [377]	0 [0]	7,723,516 [52,292]
MSD K.K.	2,224,616 [15,062]	946,647 [6,409]	2,338,771 [15,835]	278,425 [1,885]	529,009 [3,582]	0 [0]	0 [0]	0 [0]	0 [0]	6,317,468 [42,772]
Sumitomo Dainippon Pharma Co., Ltd.	478,658 [3,241]	1,926,703 [13,045]	2,712,881 [18,368]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959 [528]	5,196,201 [35,181]

Nippon Kayaku Co., Ltd.	974,487 [6,598]	958,195 [6,487]	55,685 [377]	855,809 [5,794]	222,740 [1,508]	0 [0]	222,740 [1,508]	0 [0]	579,124 [3,921]	3,868,780 [26,194]
Astellas Pharma Inc.	600,000 [4,062]	340,000 [2,302]	1,400,000 [9,479]	100,000 [677]	0 [0]	0 [0]	1,100,000 [7,448]	0 [0]	50,000 [339]	3,590,000 [24,306]
Nippon Shinyaku Co., Ltd.	33,411 [226]	33,411 [226]	2,851,072 [19,303]	0 [0]	0 [0]	0 [0]	211,603 [1,433]	0 [0]	0 [0]	3,129,497 [21,188]
Asahi Kasei Pharma Corporation	77,959 [528]	326,155 [2,208]	2,138,304 [14,477]	0 [0]	0 [0]	0 [0]	111,370 [754]	0 [0]	448,664 [3,038]	3,102,452 [21,005]
Sanofi K.K.	0 [0]	312,500 [2,116]	960,000 [6,500]	370,000 [2,505]	100,000 [677]	0 [0]	750,000 [5,078]	0 [0]	100,000 [677]	2,592,500 [17,552]
Otsuka Holdings Co., Ltd.[e]	100,000 [677]	770,000 [5,213]	1,087,912 [7,366]	0 [0]	46,286 [313]	0 [0]	0 [0]	0 [0]	200,000 [1,354]	2,204,198 [14,923]
Mochida Pharmaceutical Co., Ltd.	0 [0]	679,357 [4,600]	790,727 [5,354]	111,370 [754]	0 [0]	0 [0]	0 [0]	0 [0]	567,987 [3,846]	2,149,441 [14,553]
Teijin Pharma Limited.	550,000 [3,724]	359,790 [2,436]	1,020,000 [6,906]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	170,000 [1,151]	2,099,790 [14,217]
AbbVie GK,	0 [0]	735,042 [4,977]	245,014 [1,659]	1,046,885 [7,088]	0 [0]	0 [0]	0 [0]	55,685 [377]	0 [0]	2,082,626 [14,100]
Shionogi & Co., Ltd.	556,848 [3,770]	443,416 [3,002]	567,160 [3,840]	206,240 [1,396]	0 [0]	0 [0]	0 [0]	0 [0]	175,304 [1,187]	1,948,968 [13,195]
Kyorin Pharmaceutical Co., Ltd.	1,443,680 [9,774]	144,368 [977]	72,184 [489]	0 [0]	0 [0]	0 [0]	206,241 [1,396]	0 [0]	51,560 [349]	1,918,033 [12,986]

Tsumura & Co.	33,411 [226]	1,347,578 [9,124]	167,055 [1,131]	55,685 [377]	0 [0]	77,959 [528]	0 [0]	0 [0]	0 [0]	1,681,688 [11,386]
Meiji Seika Pharma Co., Ltd.	649,656 [4,398]	154,680 [1,047]	278,424 [1,885]	103,120 [698]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]	1,289,000 [8,727]
Terumo Corporation	110,440 [748]	585,332 [3,963]	77,308 [523]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	441,760 [2,991]	1,214,840 [8,225]
Kissei Pharmaceutical Co., Ltd.	222,740 [1,508]	55,685 [377]	0 [0]	0 [0]	0 [0]	0 [0]	144,781 [980]	0 [0]	701,634 [4,750]	1,124,840 [7,616]
Zeria Pharmaceutical Co., Ltd.	77,959 [528]	645,946 [4,373]	222,740 [1,508]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	946,645 [6,409]
Mitsubishi Tanabe Pharma Corporation	77,959 [528]	712,768 [4,826]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]	935,508 [6,334]
EA Pharma Co., Ltd.	0 [0]	752,776 [5,097]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	30,936 [209]	783,712 [5,306]
Taisho Toyama Pharmaceutical Co., Ltd.	590,261 [3,996]	0 [0]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959 [528]	701,631 [4,750]
Kowa Company, Ltd.	0 [0]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	556,851 [3,770]	590,262 [3,996]
Hisamitsu Pharmaceutical Co., Inc.	22,274 [151]	89,096 [603]	0 [0]	167,055 [1131]	0 [0]	15,591 [106]	0 [0]	0 [0]	245,014 [1,659]	539,030 [3,649]
Novo Nordisk Pharma Ltd.	0 [0]	0 [0]	474,360 [3,212]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	474,360 [3,212]

Sanwa Kagaku Kenkyusho Co., Ltd.	0 [0]	0 [0]	445,480 [3,016]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	445,480 [3,016]
Aska Pharmaceutical Co., Ltd.	0 [0]	111,370 [754]	0 [0]	77,959 [528]	0 [0]	33,411 [226]	144,781 [980]	0 [0]	55,685 [377]	423,206 [2,865]
Shire Japan K.K	0 [0]	0 [0]	367,521 [2,488]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	367,521 [2,488]
Nihon Pharmaceutical Co., Ltd.	0 [0]	0 [0]	245,014 [1,659]	0 [0]	0 [0]	0 [0]	33,411 [226]	33,411 [226]	0 [0]	311,836 [2,111]
Nippon Chemiphar Co., Ltd.	0 [0]	167,055 [1,131]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]	278,425 [1,885]
Ayumi Pharmaceutical Corporation	226,864 [1,536]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	226,864 [1,536]
Mylan Seiyaku Ltd.	0 [0]	206,240 [1,396]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	206,240 [1,396]
Kracie Holdings, Ltd.	0 [0]	30,936 [209]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]	134,056 [908]
GlaxoSmithKline K.K.	111,370 [754]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]
Minophagen Pharmaceutical Co.	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	110,440 [748]	0 [0]	110,440 [748]
Maruho Co., Ltd.	0 [0]	103,120 [698]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]

Torii Pharmaceutical Co., Ltd.	0 [0]	0 [0]	51,130 [346]	0 [0]	0 [0]	0 [0]	0 [0]	51,130 [346]	0 [0]	102,260 [692]
EN Otsuka Pharmaceutical Co., Ltd.[c]	0 [0]	89,096 [603]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	89,096 [603]
Kaken Pharmaceutical Co., Ltd.	0 [0]	0 [0]	0 [0]	77,959 [528]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959 [528]
Toray Industries, Inc.	0 [0]	0 [0]	0 [0]	77,080 [522]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,080 [522]
Santen Pharmaceutical Co., Ltd.	0 [0]	0 [0]	51,560 [349]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	51,560 [349]
Toyama Chemical Co., Ltd.	33,410 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	33,410 [226]
Total	216,806,522 [1,467,884]	139,690,202 [945,770]	119,219,713 [807,175]	49,287,661 [333,701]	9,213,401 [62,379]	570,533 [3,863]	7,862,285 [53,231]	562,502 [3,808]	42,240,495 [285,988]	585,453,314 [3,963,800]

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1.

Supplementary Material 3. List of oncology drugs with Japanese domestic sales of at least ¥5 billion [£33.9 million] in 2016

Pharmaceutical company	Drug name	2016 Sales (Billion, ¥)†	2016 Sales (Million, £)†	Respirology	Gastroenterology	Hematology	Breast	Head and neck	Gynaecology	Urology	Dermatology	Other
Astellas Pharma Inc.	Enzalutamide	23.4	158.4	No	No	No	No	No	No	Yes	No	No
Chugai Pharmaceutical Co., Ltd.	Bevacizumab	92.1	623.6	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
Chugai Pharmaceutical Co., Ltd.	Trastuzumab	34.1	230.9	No	Yes	No	Yes	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Rituximab	32.1†	217.3†	No	No	Yes	No	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Capecitabine	12.3	83.3	No	Yes	No	Yes	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Pertuzumab	11.9	80.6	No	No	No	Yes	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Alectinib	11.9	80.6	Yes	No	No	No	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Erlotinib	11.5	77.9	Yes	Yes	No	No	No	No	No	No	No
Chugai Pharmaceutical Co., Ltd.	Trastuzumab Emtansine	8.3	56.2	No	No	No	Yes	No	No	No	No	No
Daiichi Sankyo Co., Ltd.	Denosumab	13.9	94.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Eisai Co., Ltd.	Eribulin	7.8	52.8	No	No	No	Yes	No	No	No	No	Yes
Eli Lilly Japan K.K.	Pemetrexed	37.3	252.5	Yes	No	No	No	No	No	No	No	No
Eli Lilly Japan K.K.	Ramucirumab	28.9	195.7	Yes	Yes	No	No	No	No	No	No	No
Nippon Boehringer Ingelheim Co., Ltd.	Afatinib	8.7	58.9	Yes	No	No	No	No	No	No	No	No
Novartis International AG	Imatinib	27.5	186.2	No	Yes	Yes	No	No	No	No	No	No
Novartis International AG	Nilotinib	20.7	140.1	No	No	Yes	No	No	No	No	No	No
Novartis International AG	Everolimus	15.1†	102.2†	Yes	Yes	No	Yes	Yes	No	Yes	No	No
Ono Pharmaceutical Co., Ltd.	Nivolumab	103.9	703.5	Yes	No	Yes	No	Yes	No	Yes	Yes	No
Taiho Pharmaceutical Co., Ltd.	Tegafur/Gimeracil/Oteracil	26.9	182.1	Yes	Yes	No	Yes	Yes	No	No	No	No
Taiho Pharmaceutical Co., Ltd.	nab-Paclitaxel	20.7	140.1	Yes	Yes	No	Yes	No	No	No	No	No
Taiho Pharmaceutical Co., Ltd.	Calcium Folinate	9.7	65.7	No	Yes	No	No	No	No	No	No	No
Taiho Pharmaceutical Co., Ltd.	Tegafur, Uracil	6.5	44.0	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No

Takeda Pharmaceutical Co., Ltd.	Leuprorelin	48.6†	329†	No	No	No	Yes	No	No	Yes	No	No
Takeda Pharmaceutical Co., Ltd.	Panitumumab	18.8	127.3	No	Yes	No	No	No	No	No	No	No
Yakult Honsha Co., Ltd.	Oxaliplatin	18.4	124.6	No	Yes	No	No	No	No	No	No	No

We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly exchange rate for 2016, namely ¥147.7 yen per £1; A coverage under the Japanese National Health Insurance scheme in specific oncology subspecialty was considered by the end of the fiscal year of 2016 (March 31, 2017); † The sales includes that used for conditions other than cancer.

Supplementary Material 4. Newly-approved oncology drugs and drugs with added indications during the fiscal years of 2015 and 2016.

Pharmaceutical company	Drug name	Date of approval	Type of approval	Type of cancer
AstraZeneca plc	Vandetanib	September 28, 2015	New approval	Thyroid cancer
AstraZeneca plc	Osimertinib	March 28, 2016	New approval	Non-small cell lung cancer
Bayer Yakuhin, Ltd.	Sorafenib	February 29, 2016	Added indication	Thyroid cancer
Bayer Yakuhin, Ltd.	Xofigo	March 28, 2016	New approval	Prostate cancer
Bristol-Myers Squibb K.K.	Ipilimumab	July 3, 2015	New approval	Melanoma
Bristol-Myers Squibb K.K.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
Bristol-Myers Squibb K.K.	Elotuzumab	September 28, 2016	New approval	Multiple myeloma
Celgene Corporation	Lenalidomide	December 21, 2015	Added indication	Multiple myeloma
Celgene Corporation	Lenalidomide	March 2, 2017	Added indication	Adult T-cell leukemia
Chugai Pharmaceutical Co., Ltd.	Capecitabine	November 20, 2015	Added indication	Gastric cancer
Chugai Pharmaceutical Co., Ltd.	Bevacizumab	May 23, 2016	Added indication	Cervical cancer
Chugai Pharmaceutical Co., Ltd.	Capecitabine	August 26, 2016	Added indication	Rectal cancer

Eisai Co., Ltd.	Eribulin	February 29, 2016	Added indication	Sarcoma
Eli Lilly Japan K.K.	Ramucirumab	May 23, 2016	Added indication	Colorectal cancer
Eli Lilly Japan K.K.	Ramucirumab	June 20, 2016	Added indication	Non-small cell lung cancer
GlaxoSmithKline K.K.	Lapatinib	November 20, 2015	Added indication	Breast cancer
Janssen Pharmaceutical K.K.	Ibrutinib	March 28, 2016	New approval	Chronic lymphocytic leukemia
Janssen Pharmaceutical K.K.	Bortezomib	June 26, 2015	Added indication	Mantle cell lymphoma
Janssen Pharmaceutical K.K.	ibrutinib	December 2, 2016	Added indication	Mantle cell lymphoma
Meiji Seika Pharma Co., Ltd.	Talaporfin	May 26, 2015	Added indication	Esophageal cancer
Minophagen Pharmaceutical Co.	Bexarotene	January 22, 2016	New approval	Cutaneous T cell lymphoma
MSD K.K.	Peginterferon Alfa-2b	May 26, 2015	Added indication	Melanoma
MSD K.K.	Pembrolizumab	September 28, 2016	New approval	Melanoma
MSD K.K.	Pembrolizumab	December 19, 2016	Added indication	Non-small cell lung cancer
Mylan Seiyaku Ltd.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
Nippon Kayaku Co., Ltd.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
Nippon Kayaku Co., Ltd.	Nogitecan	November 20, 2015	Added indication	Cervical cancer
Novartis Pharma K.K.	Panobinostat	July 3, 2015	New approval	Multiple myeloma

Novartis Pharma K.K.	Ruxolitinib	September 24, 2015	Added indication	Polycythemia vera
Novartis Pharma K.K.	Dabrafenib	March 28, 2016	New approval	Melanoma
Novartis Pharma K.K.	Trametinib	March 28, 2016	New approval	Melanoma
Novartis Pharma K.K.	Ceritinib	March 28, 2016	New approval	Non-small cell lung cancer
Novartis Pharma K.K.	Everolimus	August 26, 2016	Added indication	Neuro-endocrine tumor
Ono Pharmaceutical Co., Ltd.	Nivolumab	February 29, 2016	Added indication	Melanoma
Ono Pharmaceutical Co., Ltd.	Nivolumab	December 17, 2015	Added indication	Non-small cell lung cancer
Ono Pharmaceutical Co., Ltd.	Carfilzomib	July 4, 2016	New approval	Multiple myeloma
Ono Pharmaceutical Co., Ltd.	Nivolumab	August 26, 2016	Added indication	Renal cell cancer
Ono Pharmaceutical Co., Ltd.	Nivolumab	December 2, 2016	Added indication	Hodgkin lymphoma
Ono Pharmaceutical Co., Ltd.	Nivolumab	March 24, 2017	Added indication	Head and neck cancer
Otsuka Pharmaceutical Co., Ltd.	Ponatinib	September 28, 2016	New approval	Chronic myelogenous leukemia
Sanofi K.K.	Plerixafor	December 19, 2016	New approval	Multiple myeloma Non-Hodgkin lymphoma Hodgkin lymphoma
Sanofi K.K.	Aflibercept Beta	March 30, 2017	New approval	Colorectal cancer

Shionogi & Co., Ltd.	Cyclophosphamide	June 26, 2015	Added indication	Malignant lymphoma
Shionogi & Co., Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
Taiho Pharmaceutical Co., Ltd.	Trabectedin	September 28, 2015	New approval	Sarcoma
Takeda Pharmaceutical Company Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
Takeda Pharmaceutical Company Ltd.	Leuprorelin	September 28, 2015	New approval	Prostate cancer Breast cancer
Takeda Pharmaceutical Company Ltd.	Ixazomib	March 30, 2017	New approval	Multiple myeloma
Yakult Honsha Company, Limited.	Oxaliplatin	November 20, 2015	Added indication	Gastric cancer

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-11
Objectives	3	State specific objectives, including any prespecified hypotheses	11
Methods			
Study design	4	Present key elements of study design early in the paper	11-16
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11-14
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	12
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14-16
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	14-16
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	14-16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	14-16
		(*b*) Describe any methods used to examine subgroups and interactions	14-16
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	14-16
		(*e*) Describe any sensitivity analyses	14-16

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	17
		(b) Give reasons for non-participation at each stage	17
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	17
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	17-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17-20
		(*b*) Report category boundaries when continuous variables were categorized	14-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	29-30
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	23-29
Generalisability	21	Discuss the generalisability (external validity) of the study results	27-29
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	32

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.