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

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Manuscripts

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15 **Pharmaceutical payments to certified oncology specialists in Japan in**
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18 **2016: a retrospective observational study**
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45 **32** Japan.
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48 **33**
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51 **34 Abstract**
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54 **35** Objective: This study aimed to elucidate the characteristics of payments from
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57 **36** pharmaceutical companies to oncology specialists in Japan, whether the
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6 37 payment was made for promotion, and whether there are specific rules to cover

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9 38 Conflict of Interest (COI) matters among the oncology specialists.

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15 40 Design, Setting, and Participants: The participants were oncology specialists

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18 41 certified by the Japanese Society of Medical Oncology (JSMO) up to 2016. We

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21 42 retrospectively extracted 2016 payment data reported by 71 Japanese

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24 43 pharmaceutical companies.

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30 45 Outcome measures: We made descriptive analyses for payments to the

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33 46 individual specialists, made generalized linear models to estimate factors

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36 47 associated with higher value payments, made a Sankey diagram to illustrate the

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39 48 payment flow from the companies to oncology subspecialties, analyzed

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42 49 oncology drugs with the annual sales of ¥5 billion [\$44,424,500] or above, and

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45 50 examined the JSMO policy for disclosing COIs.

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51 52 Results: The total and mean monetary value of payments from pharmaceutical

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54 53 companies was ¥598,286,743 [\$5,315,718], and ¥553,457 [\$4,917] (standard

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57 54 deviation ¥1,264,398 [\$11,234]), respectively. Of the 1081 specialists sampled,

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6 55 779 (72.1%) received a payment. Of this total, 147 (13.6%) receiving a payment
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9 56 of at least ¥100,000 [\$8,918] received 72.5% of the total payment (¥433,622,808
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12 57 [\$3,852,695]). In the generalized linear models, working for a university hospital
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15 58 (IRR=2.43, 95% CI=1.78–3.31) was a key factor associated with larger monetary
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18 59 payments. the payment was likely to made toward the specialties with
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21 60 high-income drugs, though its tendency differed between companies.

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24 61 Oncologists were not required to disclose any COIs related to their work.
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30 63 Conclusion: Substantial financial relationships were observed between
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33 64 pharmaceutical companies and oncology specialists, but their extents varied
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36 65 significantly between individuals. The oncology specialists were not required to
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39 66 disclose any COIs related to their work.
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45 68 **Keywords:** conflicts of interest; oncology specialist; Japan; industry payment;
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48 69 Japanese Society of Medical Oncology
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54 71 **Article summary (Strengths and limitations of this study):**
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6 72 ✓ To the best of our knowledge, this study is the first to investigate individual
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9 73 payment value of the certified oncology specialists both in Japan and
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12 74 worldwide.
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15 75 ✓ The authors independently organized the payment data published by the
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18 76 major pharmaceutical companies, and created a single uniform database for
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21 77 the payment.
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24 78 ✓ This study only covered the payment data in 2016, which hampered a
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27 79 longitudinal analysis of the type and value of the payment among the
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30 80 oncology specialists.
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82 **Word count:** 3,069

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84 **Introduction**

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

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6 90 poor or excessive nutrition and the like cancer became an ever-increasing and
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9 91 major problem.⁷ The pharmaceutical industry therefore adopted a new business
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12 92 model, discovery and development of anticancer agents which could be sold at
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15 93 extremely high price, but usually for short treatment durations.¹⁻³ This
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18 94 guaranteed a hefty profit in a short timeframe, provided that the drugs would be
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21 95 prescribed and used, while imposing an extraordinarily high cost to the
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24 96 patients.^{1-3 8} Indeed, a single administration of tisagenlecleucel, a
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27 97 recently-approved chimeric antigen receptor T-cell immunotherapy
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30 98 manufactured by Novartis Pharma, reportedly costs \$475,000.⁹
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36 100 Physicians remain paramount decision-makers on the demand-side of the
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39 101 pharmaceutical market. Even subtle financial interactions between physicians
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42 102 and a pharmaceutical company are known to affect their prescribing
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45 103 behavior,¹⁰⁻¹⁵ and could encourage irrational or preferential use of a company's
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48 104 drug. Unsurprisingly, oncologists have recently become primary targets for
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51 105 approaches from companies with high-cost anticancer products to sell. Indeed,
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54 106 significant financial relationships between such companies and the authors of
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57 107 the Clinical Practice Guideline (CPG) issued by the National Comprehensive
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6 108 Cancer Networks (NCCN) have been reported.¹⁶ Given these murky
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9 109 circumstances, there has been a growing need for intervention, in the form of
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12 110 policy implementation and education about the implications of these interactions
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15 111 to help protect doctors, patients, institutions and the companies themselves.¹²⁻¹⁵
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18 112 Consequently, medical and governmental facilities worldwide are considering
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21 113 guidelines, self-regulation and legislative checks to help control the relationship
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24 114 between physicians and the pharmaceutical industry, exemplified by the USA's
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27 115 Physician Payments Sunshine Act, enacted in 2010.^{17 18}
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33 117 Although Japan has the third largest pharmaceutical market, with annual
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36 118 pharmaceutical sales of \$76 billion in 2017,¹⁹ its overall scale has been declining
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39 119 at approximately 2% annually.²⁰ To maintain sales in these competitive and
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42 120 tightening markets, forceful advertisement of high-price products, namely novel
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45 121 oncology drugs, has become increasingly important for pharmaceutical
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48 122 companies. Indeed, sales of oncology drugs have recently been rising in Japan,
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51 123 exceeding ¥1 trillion [\$8.9 billion] for the first time in 2016.²¹ Furthermore, sales
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54 124 are predicted to increase 1.5-fold in the next decade with the increasing
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57 125 application of immunotherapy in clinical practice.²¹ It would be reasonable to
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6 126 assume that pharmaceutical companies will increasingly deploy marketing
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9 127 measures and incentives targeting oncology specialists for the immediate and
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12 128 foreseeable future.
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18 130 In Japan, the Japan Pharmaceutical Manufacturers Association (JPMA) has
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21 131 made details of pharmaceutical company payments publicly available since
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24 132 fiscal year 2013.²² The aim was to improve the transparency of linkages
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27 133 between pharmaceutical companies and physicians, as in the USA's Physician
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30 134 Payments Sunshine Act,^{17 18} the transparency surrounding payment disclosures
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33 135 in Japan being traditionally very poor, with examination of company/physicians
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36 136 links and payments in a meaningful way proving almost impossible. Furthermore,
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39 137 little was known about regulations concerning oncologists having to declare
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42 138 details with respect to Conflicts of Interest (COIs) that could affect their work.
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48 140 The aims of the current study were: 1) to understand and evaluate the
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51 141 characteristics and distributions of financial payments made by pharmaceutical
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54 142 companies to oncology specialists: 2) to examine a well-accepted belief that
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57 143 pharmaceutical companies make payments to promote their products; and 3) to
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6 144 elucidate whether Japanese oncology specialists are obliged in any way to

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9 145 disclose their COIs.

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15 147 **Methods**

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18 148 *Study setting and participants*

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21 149 We included all oncology specialists certified by the Japanese Society of
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24 150 Medical Oncology (JSMO) as of the beginning of April 1, 2016. The JSMO, with
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27 151 9,154 members in 2017, is the largest professional medical society in the
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30 152 oncology field in Japan. The JSMO began operating a specialty recording
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33 153 system for members in 2004. In general, Japanese certified oncologists have
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36 154 strong discretionary power with respect to their prescribing of oncology drugs, as,
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39 155 in the past, only these physicians were allowed to prescribe specific agents,
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42 156 such as nivolumab and gefitinib.

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48 158 *Sources of Payment Data*

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51 159 We collected payment data, as published by all 71 companies that belonged to
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54 160 the JPMA. For most eligible companies, the 2016 data was the most recent, with
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57 161 previous payment data being unavailable. The companies included in this study,

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6 162 plus the starting and ending dates of their payment data, are listed in
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9 163 Supplementary Material 1.
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15 165 We obtained each company's data and organized them into a unified single
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18 166 database as follows; first, because no data was published as a spreadsheet,
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21 167 data with character codes was converted into a spreadsheet format. Second,
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24 168 data with no character code was converted into text files using an Optical
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27 169 Character Reader. Third, when data was protected against facsimile or
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30 170 reproduction, we used FullShot10 software (Inbit, CA, USA) to scan photos of
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33 171 the data and converted the data into text files. Finally, we confirmed the
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36 172 accuracy of the organized data by comparing it with the original data. The
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39 173 database included physicians' names, their main institutions, payments received,
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42 174 the form of the payments, and the total amount of payments. The form of
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45 175 payment was categorized into three types; payment for speaking, payment for
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48 176 writing, and consulting fees.

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54 178 *Data collection*
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6 179 We examined payment data for all oncology specialists included in this study.
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9 180 Further, we determined their main working institution and region, along with the
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12 181 year of their certification from the JSMO website. We further extracted the
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15 182 subspecialties (respiratory, gastroenterology, hematology, breast, etc.) of all
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18 183 individuals who received a payment of ¥1 million [\$8,885] or above from any
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21 184 pharmaceutical company, collating data from institutional websites using an
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24 185 internet search engine (Google). In general, ¥1 million [\$8,885] is approximately
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27 186 25% of the median annual income of a Japanese citizen.²³ In addition, we
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30 187 attempted find any COI policy from the JSMO website.
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36 189 *Data analysis*
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39 190 To examine the characteristics and distributions of payments, we performed
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42 191 descriptive analyses of the data on an individual oncology specialist and
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45 192 pharmaceutical company basis. We then specifically summarized the
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48 193 characteristics of oncology specialists receiving a total payment of ¥1 million
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51 194 [\$8,885] or above. Using a multivariate negative binomial regression model, we
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54 195 subsequently examined possible factors associated with the monetary value of
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57 196 the payment to the individual oncologists, using working institutions, working
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6 197 regions, and year of experience after the board certification as covariates. The
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9 198 payment data was rounded off as a unit of ¥1 million [\$8,885]. Further, to assess
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12 199 the effects of the subspecialty on the value of the payment, using a
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15 200 zero-truncated negative binomial model, we repeated the analysis among those
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18 201 receiving payments of ¥1 million [\$8,885] or above. Second, to confirm whether
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21 202 the payment was made for promotional purposes, we created a Sankey diagram
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24 203 among the specialists in this cohort to illustrate the distribution of the payment to
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27 204 each subspecialty on an individual company basis. The Sankey diagram is a
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30 205 flow diagram, where band width proportionally represents the flow quantity.²⁴
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33 206 Payment values from individual companies, according to subspecialty, are
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36 207 depicted in the bands in the diagram, width being proportional to the total
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39 208 amount of the payment. In addition, to see whether the payment was linked to
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42 209 any specific oncology drugs, we examined such drugs with annual Japanese
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45 210 domestic sales of ¥5 billion [\$44,424,500] or above, and if each drug was
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48 211 covered in the Japanese National Health Insurance scheme in 2016. We
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51 212 converted Japanese yen (¥) to US dollars (\$) using the October 21, 2018
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54 213 exchange rate of ¥113 yen per US\$1.
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6 215 *Ethics approval*
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9 216 This study was approved by the Institutional Review Board of Medical
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12 217 Governance Research Institute (MEGRI) on 16 May 2018.
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18 219 *Patient and Public Involvement*
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21 220 The present study is a retrospective analysis of the existing database, and we
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24 221 did not include the patients and other population in particular in the development
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27 222 of the study design.
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33 224 *Role of the funding source*
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36 225 The funders – Ain Pharmaciez Inc. and Waseda Chronicle made no contribution
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39 226 whatsoever to either the design of the study, the work carried out or the
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42 227 interpretation of the study findings.
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48 229 **Results**
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51 230 Table 1 summarizes the details of certified oncology specialists and payments
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54 231 from Japanese pharmaceutical firms. Of 1081 eligible certified oncology
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6 232 specialists, 315 (29.1%), 142 (13.1%), and 407 (37.7%) worked for university
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9 233 hospitals, cancer hospitals, and other general hospitals, respectively.
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15 235 The total monetary value of the payments made was ¥598,286,743 [\$5,315,718],
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18 236 entailing 7,445 payments. The mean and median monetary value of an
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21 237 individual payment was ¥553,457 [\$4,917] (standard deviation (SD) ¥1,264,398
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24 238 [\$11,234]) and ¥122,507 [\$1,088] (interquartile range (IQR) ¥ 0–445,480 [\$0–
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27 239 3,958]), respectively. Similarly, the mean and median figure for the number of
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30 240 individual payments was 7 (SD 13) and 2 (IQR 0–7), respectively. The number of
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33 241 oncology specialists receiving any payment was 779 (72.1%). Of the 1081
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36 242 participants, 147 (13.6%) received payments totaling ¥1 million [\$8,885] or more.
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39 243 while 20 (1.9%) received ¥5 million [\$44,425] or above. Only 3 (0.2%) received
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42 244 ¥10 million [\$88,849] or above.
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48 246 A summary of payments of 56 companies which made any payment to the
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51 247 oncologists is shown in Table 2. The Chugai Pharmaceutical Co. Ltd., a
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54 248 subsidiary of F. Hoffmann-La Roche Ltd, made the largest total payment of
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57 249 ¥103,727,395 [\$921,608], while Toyama Chemical Co., Ltd. paid the lowest
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6 250 (¥33,410 [\$297]). The mean and median monetary value among the companies
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9 251 was ¥10,877,941 [\$96,649] (SD ¥19,041,596 [\$169,183]) and ¥2,099,790
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12 252 [\$18,656] (IQR ¥423,206–15,207,296 [\$3,760–135,115]), respectively.
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18 254 Table 3 summarizes the characteristics of specialists receiving a total payment
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21 255 of ¥1 million [\$8,885] and above. Overall, 50.3% worked for university hospitals,
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24 256 and 19.0% were certified within the last five years (2012–2016). The top three
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27 257 subspecialties attracting payments were respiratory (56 (38.1%)),
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30 258 gastroenterology (36 (24.5%)), and hematology (27 (18.4%)). The total
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33 259 monetary value and count was ¥433,622,808 [\$3,852,695] and 4,606,
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36 260 respectively accounting for 72.5% and 61.9% of the totals, with respiratory
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39 261 attracting (¥177,274,111 [\$1,575,062] (40.9%)), gastroenterology (¥100,424,612
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42 262 [\$892,262] (23.2%)) and hematology (¥81,649,310 [\$725,446] (18.8%)).
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48 264 Table 4 displays findings of the multivariate regression analyses for the
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51 265 monetary value of payments. Oncologists with longer experience after board
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54 266 certification (incidence rate ratio (IRR)=1.30, 95% CI=1.23–1.37, p<0.001) and
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57 267 those working for university hospitals (IRR=2.43, 95% CI=1.78–3.31, p<0.001)
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6 268 were significantly more likely to receive larger payments compared with their
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9 269 counterparts. Similar trends were observed for those with payment values of ¥1
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12 270 million [\$8,885] or above. Those working in the respiratory subspecialty were
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15 271 likely to receive higher payments compared with all others, although this trend
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18 272 was not statistically significant.

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24 274 Figure 1 displays payment distributions to each subspecialty on an individual
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27 275 company basis. Details of the payments are provided in Supplementary Material
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30 276 2. Further, in Table 5, we summarize the list of oncology drugs with Japanese
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33 277 domestic sales of ¥5 billion [\$44,424,500] or more. Chugai Pharmaceutical Co.,
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36 278 Ltd. made the largest subspecialty payment of ¥74,542,676 [\$662,304], and the
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39 279 top four subspecialties were respiratory (¥25,061,169 [\$222,666], 33.6%),
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42 280 gastroenterology (¥24,264,112 [\$215,584], 32.6%), hematology (¥14,242,968
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45 281 [\$126,547], 19.1%), and breast (¥8,958,305 [79,594]. 12.0%). The Chugai
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48 282 company manufactured eight oncology drugs with annual sales of ¥5 billion
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51 283 [\$44,424,500] or more (Table 5), and three, four, one, and five drugs were
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54 284 respectively covered in under the National Health Insurance scheme in
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57 285 respiratory, gastroenterology, hematology, and breast subspecialties. Nivolumab,
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6 286 manufactured by the Ono Pharmaceutical Co., Ltd., and used in respiratory and
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9 287 dermatology subspecialties, had the largest domestic sales in 2016 (¥103.9
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12 288 billion [\$923,141,110]). The total monetary value of the company's payments
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15 289 was ¥36,906,340 [\$327,909] (representing third place in the payment table), of
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18 290 which ¥24,623,912 [\$218,781] (66.7%) was specifically distributed to the
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21 291 respiratory subspecialty.
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27 293 The COI policy of the JSMO does not mention how oncology specialists should
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30 294 disclose their financial relationships with pharmaceutical industry enterprises
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33 295 and they do not have to report any financial relationships to the JSMO or
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36 296 publicly.
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298 **Discussion**

45 299 In this study, approximately ¥600 million [\$5,330,940] was paid by Japanese
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48 300 pharmaceutical companies to around 70% of the 1081 certified oncology
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51 301 specialists, all of whom were under no obligation to disclose the payments.
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54 302 Payments were concentrated on specific targets, notably oncologists working for
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57 303 university hospitals.
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9 305 Compared to past studies, the proportion of certified oncologists receiving
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12 306 payments was larger than for general physicians in the US (48.0%)²⁵ and Japan
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15 307 (33.3%).²⁶ The proportion was only slightly smaller than that of NCCN oncology
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18 308 CPG authors in the US (86.4%).¹⁶ Although the mean value of payments in our
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21 309 study was approximately half of that of the CPG authors (\$4,917 vs.\$10,011), a
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24 310 simple comparison is not valid as our analysis did not include stock ownership,
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27 311 investment interest, or payments from medical device companies.²⁵ The CPG
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30 312 authors strongly influence oncology practice both in the US and internationally,²⁷
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33 313 by recommending treatment algorithms. They thus become prime targets for
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36 314 influence from pharmaceutical companies selling anticancer products. It is clear
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39 315 that Japanese pharmaceutical companies with similar anticancer interests would
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42 316 target oncology specialists and attempt to boost the sales and use of their
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45 317 specific products.

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51 319 We observed a large disparity in payments to specialists. Those receiving ¥1
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54 320 million or more accounted for 13.6% of the total participating but received 72.5%
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57 321 of the total paid. Companies appear to have consciously targeted their funds to

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6 322 maximize promotion of their products, but not as expected. Oncologists working
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9 323 for university hospitals were more likely to receive a larger value payment. But in
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12 324 Japanese medical circles, cancer centers are generally more likely to treat more
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15 325 cancer patients compared to university hospitals. Indeed, cancer centers top the
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18 326 nationwide ratings for treatments in most of the common cancers, including lung,
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21 327 colon, gastric, and breast cancer.²⁸ In contrast, university hospitals are regarded
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24 328 as symbols of academic excellence and authority, and medical school
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27 329 professors traditionally have a strong influence on both physicians and medical
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30 330 practice in their field of expertise. Thus, our findings suggest that Japanese
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33 331 pharmaceutical companies have placed greater emphasis on expertise and
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36 332 authority, compared with clinical experience, in the selection of targets for their
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39 333 promotional activities.

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45 335 We found that the respiratory subspecialty attracted the greatest financial outlay.
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48 336 In Japan, this field covers a large patient volume and involves multiple novel
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51 337 oncology drugs, such as nivolumab (Ono Pharmaceutical Co., Ltd, (approved
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54 338 2015)), pembrolizumab (MSD K.K., (2016)), alectinib (Chugai Pharmaceutical
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57 339 Co., Ltd., (2014)), osimertinib (AstraZeneca plc, (2016)), ramcirumab (Eli Lilly
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6 340 Japan K.K., (2016)), and afanitinib (Nippon Boehringer Ingelheim Co., Ltd.,
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9 341 (2016)), all for non-small cell lung cancer. As such, for the pharmaceutical
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12 342 companies, this field is a critical yet highly competitive target in any strategy to
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15 343 maximize the cost-effectiveness of their promotional endeavors.
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21 345 The examples of Chugai Pharmaceutical and Ono Pharmaceutical confirm the
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24 346 belief that there is an association between the value and destination of
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27 347 payments dependent on the products the companies in question manufacture.
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30 348 AstraZeneca may, from our findings, be an exception to this rule. While it made
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33 349 the second largest total payments to physicians with a known subspecialty
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36 350 (¥43,836,859 [\$389,486]), it did not have any oncology drugs providing a high
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39 351 income. However, it does sell an immunotherapy agent dulvalumab, which was
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42 352 covered by the National Health Insurance scheme for treating non-small cell
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45 353 lung cancer in 2018. Thus, it is reasonable to assume that funds were allocated
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48 354 to promote their forthcoming product and engage and incentivize key individuals
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51 355 for future relationships. Indeed, 86% of the company's payment was allocated to
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54 356 the respiratory subspecialty.
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6 358 Surprisingly, there is no clear rule for COI disclosure among Japanese oncology
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9 359 specialists. As we have demonstrated, there is an emphatic financial relationship
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12 360 between pharmaceutical companies and oncologists, which to many would
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15 361 appear unhealthy or of a somewhat dubious nature. It is true that the receipt of
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18 362 the abovementioned payments in Japan is not illegal, as they are supposedly
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21 363 given as remuneration for lectures, writing and consultations. However, we
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24 364 believe that there is an ethical problem inherent in such relationships, given that
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27 365 this practice could have developed to possibly end up expanding the profit of
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30 366 pharmaceutical companies, rather than promoting the health and well-being of
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33 367 patients. Indeed, even a subtle but reputable financial relationship with the
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36 368 industry, such as collaborating in a field trial, could bias the physicians'
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39 369 prescription patterns in a manner that benefits the companies.¹⁰⁻¹⁵ Oncologists in
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42 370 Japan handle extraordinary and very potent life-saving drugs, and have a
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45 371 degree of autonomy in their prescribing actions. Their decisions substantially
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48 372 influence the treatment and outcome for their patients, as well as having
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51 373 significant economic impact due to the high cost of anticancer medications.¹⁻³ It
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54 374 would therefore appear sensible to have rigorous regulations to cover the open
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57 375 and accessible reporting of any financial dealings between physicians and
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6 376 pharmaceutical companies so as to avoid any potential nefarious or underhand
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9 377 behavior or undue pressure on physicians to alter their usual treatment practices.
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12 378 Indeed, it is possible that these highly-questionable arrangements may have
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15 379 contributed to the multiple cases of scientific misconduct that have recently been
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18 380 reported in Japan. The most infamous case was when employee misconduct
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21 381 was discovered in a series of clinical trials for Valsartan, an antihypertensive
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24 382 medication manufactured by Novartis Pharma, leading to a retraction of the
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27 383 associated academic papers.^{29 30} A breast cancer clinical trial (CREATE-X trial)
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30 384 with a questionable pharmaceutical payment has also been identified.^{31 32}
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36 386 To prevent similar cases in future, we call for the implementation of a
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39 387 transparent, independent mechanism that would enable a comprehensive
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42 388 assessment of any and all payments being made by any pharmaceutical
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45 389 company to any individual physician or, for that matter, medical institution where
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48 390 the company's products may be used, and not just with respect to oncology.
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51 391 New schemes, such as the US's Open Payments, may prove successful but it is
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54 392 too soon to know.³³ The Disclosure UK mechanism may not prove so useful as it
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57 393 is voluntary. Additionally, given that such mechanisms allow for direct
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6 394 comparison between what is allegedly paid and what is allegedly received, it will
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9 395 necessitate a fair, equitable and timely mechanism for dispute settlement,
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12 396 probably involving the use of third parties. ³²
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18 398 **Conclusion**

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21 399 Japanese certified oncologists receive financial payments direct from
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24 400 pharmaceutical companies, usually from those active in the specialist field of the
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27 401 physician in question. This raises several queries with regard to ethical, medical
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30 402 and possibly legal issues. The value and speciality targets of the payments
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33 403 varied substantially which also raises yet more questions as to why. We believe
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36 404 that the lessons learned from our analyses should be shared among the global
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39 405 medical community to put in place safeguards to prevent undue and unethical
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42 406 inducements from the pharmaceutical industry and to help protect physicians
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45 407 from outside influences. It is essential to establish a robust, comprehensive and
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48 408 binding system for identifying and avoiding any and all potential conflicts of
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51 409 interest, of any nature, involving physicians or other medical professionals, both
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54 410 in Japan and internationally.
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412 **Author contributors:**

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

415 All authors were involved in the study concept and design:

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

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

419

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428

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5
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7
8
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13
14
15 433 authors declare no conflict of interests.
16

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33 439 **Data sharing statement:**

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36 440 The datasets analysed during the current study are available from the
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38
39 441 corresponding author on reasonable request.
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45 443 **Figure legends:**

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48 444 **Figure 1. Distribution of payments to each subspecialty on an individual**

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51 445 **company basis.** The companies and specialties are sorted in descending order
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54 446 with regard to payment value (proportionally expressed in the box height and
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57 447 band width in Figure 1). Band colour represents the payment destination
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6 448 specialties. Due to space limitations, names of companies with payment values
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9 449 of less than ¥10 million [\$8,885] have been omitted.
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For peer review only

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

Variable	
<u>1. Characteristics of oncology specialists (N=1081)</u>	
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)
<u>2. Characteristics of pharmaceutical company payments</u>	
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

573

574 **Table 3. Characteristics of oncology specialists (receiving ¥1 million or**
 575 **more) and pharmaceutical company payments received by this group in**
 576 **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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579 **Table 4. Multivariate regression models for the monetary value of payment**580 **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)

581 † Other subspecialties included Urology and Head and neck cancer. Due to the

582 small number of physicians in these two subspecialties, they were included in

583 the “other” category.

584 IRR=Incidence rate ratio, CI=Confidence interval

585 * <0.05, ** <0.01, *** <0.001

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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-Paclitaxel	20.7	Yes	Yes	No	Yes	No	No	No
Taiho Pharmaceutical Co., Ltd.	Calcium Folate	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

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

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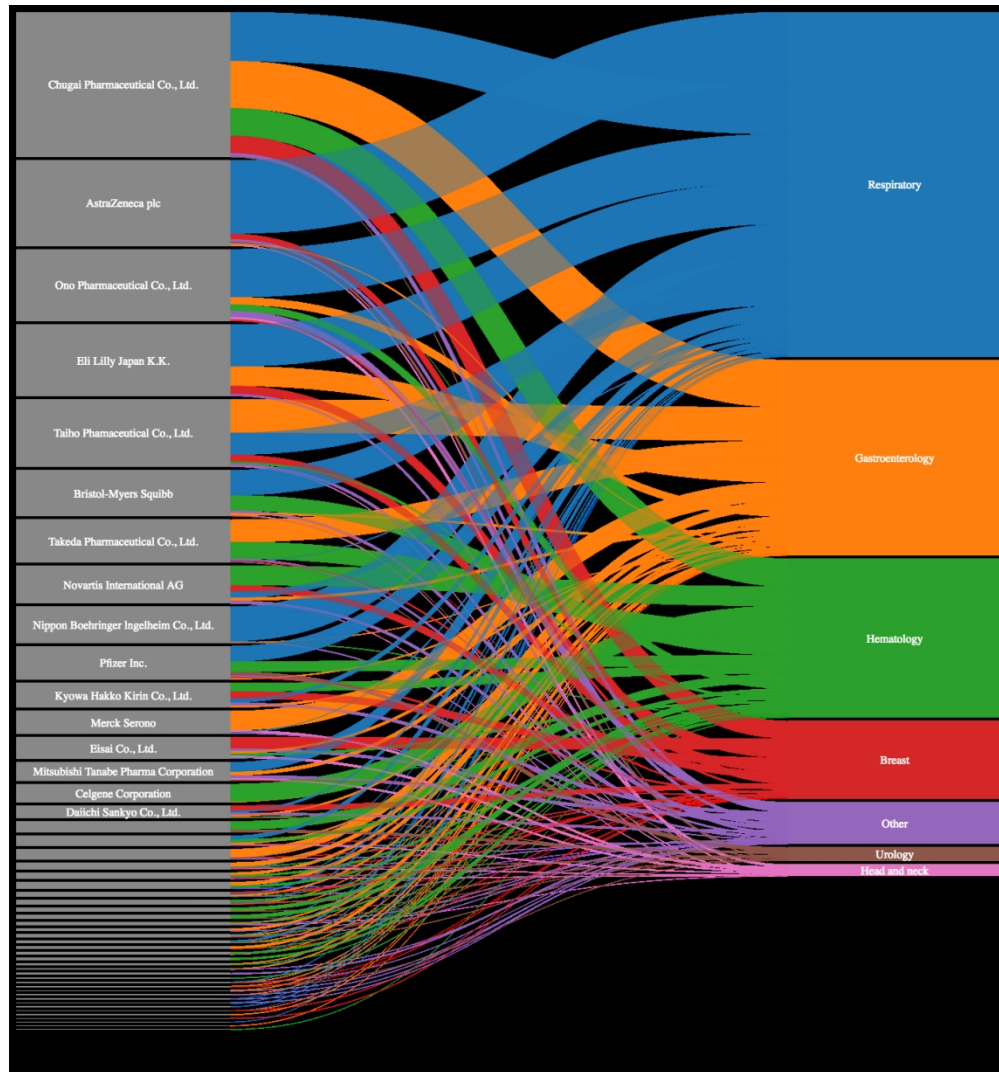


Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band colour represents the payment destination specialties.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

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6	ASAHI KASEI PHARMA CORPORATION,	April 1, 2016	March 31, 2017
7	Wakamoto Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
8			
9	MOCHIDA PHARMACEUTICAL CO., LTD.,	April 1, 2016	March 31, 2017
10			
11	Santen Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
12			
13	Mylan Seiyaku Ltd.,	January 1, 2016	December 31, 2016
14			
15	Yakult Honsha Company, Limited.,	April 1, 2016	March 31, 2017
16			
17	Minophagen Pharmaceutical Co.,	April 1, 2016	March 31, 2017
18			
19	Taisho Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
20			
21	ASKA Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
22			
23	Meiji Seika Pharma Co., Ltd.,	April 1, 2016	March 31, 2017
24			
25	NIHON PHARMACEUTICAL CO., LTD.,	April 1, 2016	March 31, 2017
26			
27	Maruishi Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
28			
29	KYORIN Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
30			
31	TEIJIN PHARMA LIMITED.,	April 1, 2016	March 31, 2017
32			
33	ZERIA Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
34			
35	SANWA KAGAKU KENKYUSHO CO., LTD.,	April 1, 2016	March 31, 2017
36			
37	Kaken Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
38			
39	Hisamitsu Pharmaceutical Co., Inc.,	March 1, 2016	February 28, 2017
40			
41	Sanofi K.K.,	January 1, 2016	December 31, 2016
42			
43	EA Pharma Co., Ltd.,	April 1, 2016	March 31, 2017
44			
45	Nippon Boehringer Ingelheim Co., Ltd.,	January 1, 2016	December 31, 2016
46			
47	Torii Pharmaceutical Co., Ltd.,	January 1, 2016	December 31, 2016
48			
49	AstraZeneca plc	January 1, 2016	December 31, 2016
50			
51	Sumitomo Dainippon Pharma Co., Ltd.,	April 1, 2016	March 31, 2017
52			
53	Novartis Pharma K.K.,	January 1, 2016	December 31, 2016
54			
55	Eli Lilly Japan K.K.,	January 1, 2016	December 31, 2016
56			
57	ONO PHARMACEUTICAL CO., LTD.,	April 1, 2016	March 31, 2017
58			
59	Kissei Pharmaceutical Co., Ltd.,	April 1, 2016	March 31, 2017
60			
	Eisai Co., Ltd.,	January 1, 2016	December 31, 2016

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6	NIPPON SHINYAKU CO., LTD.,	April 1, 2016	March 31, 2017
7	AbbVie GK,	January 1, 2016	December 31, 2016
8	Mitsubishi Tanabe Pharma Corporation,	April 1, 2016	March 31, 2017
9	Research Institute for Microbial Diseases,	April 1, 2016	March 31, 2017
10	MSD K.K.,	January 1, 2016	December 31, 2016
11	Janssen Pharmaceutical K.K.,	January 1, 2016	December 31, 2016
12	Kyowa Hakko Kirin Company, Limited,	January 1, 2016	December 31, 2016
13	Takeda Pharmaceutical Company Limited.,	April 1, 2016	March 31, 2017
14	TAIHO PHARMACEUTICAL CO., LTD.,	January 1, 2016	December 31, 2016
15	Otsuka Pharmaceutical Co., Ltd.,	January 1, 2016	December 31, 2016
16	DAIICHI SANKYO COMPANY, LIMITED.,	April 1, 2016	March 31, 2017
17	GlaxoSmithKline K.K.,	January 1, 2016	December 31, 2016
18	Shionogi & Co., Ltd.,	April 1, 2016	March 31, 2017
19	Chugai Pharmaceutical Co., Ltd.,	January 1, 2016	December 31, 2016
20	Novo Nordisk Pharma Ltd.,	January 1, 2016	December 31, 2016
21	Astellas Pharma Inc.,	April 1, 2016	March 31, 2017
22	Pfizer Japan Inc.,	December 1, 2015	November 30, 2016
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5 **Supplementary Material 2. Monetary value of payment (¥) in each company according to oncology subspecialty**

6 Company name	Respiratory	Gastroenterology	Hematology	Breast	Urology	Head and neck	Other	All
8 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
9 10 AstraZeneca plc	37,680,325	662,651	55,685	2,770,885	890,960	456,618	1,319,735	43,836,859
11 Ono Pharmaceutical Co., Ltd.	24,623,912	3,718,073	3,396,785	890,961	0	1147112	3,129,497	36,906,340
12 13 Eli Lilly Japan K.K.	21,566,802	9,944,828	0	4,145,014	0	0	1,046,878	36,703,522
14 15 Taiho Pharmaceutical Co., Ltd.	11,248,370	17,134,599	1,202,796	3,530,431	0	222740	1,147,111	34,486,047
16 17 Bristol-Myers Squibb	13,019,156	1,058,015	7,735,684	33,411	278,426	300,699	1,314,166	23,739,557
18 Takeda Pharmaceutical Co., Ltd.	411,752	11,462,655	8,531,978	523,439	171,829	0	798,682	21,900,335
19 20 Novartis International AG	3,140,636	1,525,769	9,913,984	3,306,435	0	77,959	1,299,619	19,264,402
21 22 Nippon Boehringer Ingelheim Co., Ltd.	17,652,164	111,370	211,370	0	0	0	445,480	18,420,384
23 24 Pfizer Inc.	7,840,157	607,127	5,257,311	764,319	1,832,840	0	767,502	17,069,256
25 26 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
27 28 Merck Serono	467,754	9,722,368	0	33,411	0	946,645	412,069	11,582,247
29 30 Eisai Co., Ltd.	445,480	1,191,660	1,180,522	5,791,243	0	1135975	1,380,988	11,125,868
31 32 Mitsubishi Tanabe Pharma Corporation	4,844,593	1,780,235	44,548	389,795	0	813,002	1,458,947	9,331,120
33 34 Celgene Corporation	0	103,120	9,085,712	0	0	0	0	9,188,832
35 36 Daiichi Sankyo Co., Ltd.	1,124,842	915,086	222,740	2,615,204	389,796	0	1,084,466	6,352,134
37 38 Janssen Pharmaceutical K.K.	0	0	4,276,610	0	1,252,917	0	0	5,529,527
39 40 MSD K.K.	1,901,643	545,715	1,748,510	278,425	0	529,009	111,370	5,114,672
41 42 Yakult Honsha Co., Ltd.	288,740	4,248,928	0	381,548	0	0	175,306	5,094,522

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5	Bayer AG	155,918	1,971,249	356,384	55,685	222,740	222,740	278,425	3,263,141
6	Sanofi K.K.	0	1,250,000	890,000	325,000	550,000	100000	50,000	3,165,000
7									
8	Sumitomo Dainippon Pharma Co., Ltd.	278,425	1,626,004	1,124,837	0	0	0	77,959	3,107,225
9									
10	Nippon Kayaku Co., Ltd.	774,021	679,357	55,685	800,124	22,274	0	122,507	2,453,968
11	Astellas Pharma Inc.	390,000	100,000	900,000	100,000	520,000	0	0	2,010,000
12									
13	Asahi Kasei Pharma Corporation	0	114,552	1,659,413	0	111,370	0	0	1,885,335
14									
15	Nippon Shinyaku Co., Ltd.	0	0	1,748,509	0	111,370	0	0	1,859,879
16	Otsuka Pharmaceutical Co., Ltd.	100,000	440,000	607,912	0	0	46286	200,000	1,394,198
17									
18	Zeria Pharmaceutical Co., Ltd.	0	1,113,700	0	0	0	0	222,740	1,336,440
19									
20	Shionogi & Co., Ltd.	360,920	329,984	309,360	103,120	0	0	134,056	1,237,440
21	Kyorin Pharmaceutical Co.,LTD.	845,584	72,184	72,184	0	206,241	0	0	1,196,193
22									
23	Tsumura & Co.	0	1,080,290	55,685	55,685	0	0	0	1,191,660
24									
25	Teijin Pharma Limited	170,000	70,000	850,000	0	0	0	0	1,090,000
26	Sanwa Kagaku Kenkyusho Co., Ltd.	0	0	890,960	0	0	0	0	890,960
27									
28	AbbVie GK	0	467,754	245,014	0	0	0	0	712,768
29									
30	Terumo Corporation	110,440	430,716	0	0	0	0	110,440	651,596
31	Kowa Company, Limited	0	0	0	0	0	0	556,851	556,851
32									
33	Novo Nordisk Pharma Ltd.	0	0	360,925	0	0	0	0	360,925
34									
35	Meiji Seika	154,680	51,560	0	51,560	0	0	72,184	329,984
36	Aska Pharmaceutical Co., Ltd.	0	111,370	0	77,959	111,370	0	0	300,699
37									
38	Nippon Chemiphar Co., Ltd.	0	167,055	0	0	0	0	111,370	278,425
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5	Kracie Pharmaceutical, Ltd.	0	61,872	0	0	0	0	206,240	268,112
6	Ayumi Pharmaceutical Corporation	154,680	0	0	0	0	0	72,184	226,864
7									
8	Kissei Pharmaceutical Co., Ltd.	111,370	0	0	0	0	0	111,370	222,740
9									
10	Teijin Home Healthcare Limited	190,000	0	0	0	0	0	0	190,000
11									
12	Hisamitsu Pharmaceutical Co., Inc.	22,274	33,411	0	111,370	0	0	0	167,055
13	EA Pharma Co.,Ltd.	0	154,680	0	0	0	0	0	154,680
14									
15	Torii Pharmaceutical Co., Ltd.	0	0	0	103,120	0	0	0	103,120
16									
17	Mochida Pharmaceutical Co., Ltd.	0	55,685	0	0	0	0	0	55,685
18									
19	Nihon Pharmaceutical Co., Ltd.	0	0	55,685	0	0	0	0	55,685
20	GlaxoSmithKline plc	55,685	0	0	0	0	0	0	55,685

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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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028805.R1
Article Type:	Research
Date Submitted by the Author:	10-Apr-2019
Complete List of Authors:	Ozaki, Akihiko; Medical Governance Research Institute; Jyoban Hospital of Tokiwa Foundation, Department of Breast Surgery Saito, Hiroaki; Sendai Kousei Hospital, Department of Gastroenterology Onoue, Yosuke; College of Humanities and Sciences, Nihon University Sawano, Toyoaki; Minamisoma Municipal General Hospital, Department of Surgery Shimada, Yuki; Minamisoma Municipal General Hospital, Department of Neurosurgery Somekawa, Yurie; Medical Governance Research Institute Tsuji, Aritsune; Medical Governance Research Institute Tanimoto, Tetsuya; Medical Governance Research Institute
Primary Subject Heading:	Ethics
Secondary Subject Heading:	Oncology, Ethics, Health policy
Keywords:	conflicts of interest, oncology specialist, Japan, industry payment, Japanese Society of Medical Oncology

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Manuscripts

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12 **Pharmaceutical payments to certified oncology specialists in Japan in 2016: a**
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15 **retrospective observational cross-sectional analysis**
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42 30 **Abstract (299 words)**

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45 31 Objective: This study aimed to elucidate the characteristics of payments from

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48 32 pharmaceutical companies to oncology specialists in Japan, whether the payment was

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51 33 made for promotional purposes, and whether there are specific rules to cover Conflict of

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54 34 Interest (COI) matters among the oncology specialists.

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6 36 Design, Setting, and Participants: The participants were oncology specialists certified
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9 37 by the Japanese Society of Medical Oncology (JSMO) up to 2016. We retrospectively
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12 38 extracted 2016 payment data reported by 78 Japanese pharmaceutical companies.
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18 40 Outcome measures: We identified payments to the individual specialists, employed
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21 41 several regression approaches to estimate factors associated with higher value
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24 42 payments, made a Sankey diagram to illustrate the payment flow from the companies to
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27 43 oncology specialties, analyzed oncology drugs with annual sales of ¥5 billion [£33.9
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30 44 million, €40.2 million, \$46.0 million] or above (hereafter high-income drugs) and
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33 45 examined the JSMO policy for oncology specialists disclosing COIs.
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39 47 Results: In total, 59 companies made at least one payment to the oncologists, and the
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42 48 total monetary value was ¥585,453,314 [£3,963,800, €4,702,436, \$5,381,005]. Of the
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45 49 1080 specialists sampled, 763 (70.6%) received at least one payment while 317 received
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48 50 no payment at all. Of the 763, a small group of 142 (13.1%) receiving at least ¥1 million
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51 51 [£6.8 thousand, €8.0 thousand, \$9.2 thousand] accounted for 71.5% of the total
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54 52 (¥418,345,258 [£2,832,398, €3,360,203, \$3,845,085]). After adjustment of covariates,
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57 53 working for university hospitals and for cancer hospitals were key factors associated
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6 54 with larger monetary payments. Payments were likely to be made toward the specialties
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9 55 using high-income drugs, though the tendency differed between companies. The JSMO
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12 56 has its own COI policy for its members but it did not specifically mention its certified
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15 57 oncology specialists.
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21 59 Conclusion: Substantial financial relationships were observed between pharmaceutical
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24 60 companies and oncology specialists, but their extents varied significantly between
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27 61 individuals. There should be specific COI rules covering oncologists.
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33 63 **Keywords:** conflict of interest; oncology specialist; Japan; industry payment; Japanese
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36 64 Society of Medical Oncology
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42 66 **Article summary (Strengths and limitations of this study):**
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45 67 ✓ We considered oncology specialists certified by the Japan Society of Medical
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48 68 Oncology, which is one of the largest professional medical associations in the
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51 69 clinical oncology field of Japan.
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6 70 ✓ The authors independently organized payment data for oratory, writing, and
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9 71 consulting work, as published by the major pharmaceutical companies, and created
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12 72 a single uniform payment database.
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15 73 ✓ Accuracy of the affiliations and subspecialties of some oncology specialist in the
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18 74 study year (2016) were estimated using the data on the affiliation websites and
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21 75 other data sources on the Internet, possibly causing some measurement errors in
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24 76 these variables.
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27 77 ✓ This study only covered limited types of payment data in the single year (2016),
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30 78 which hampered a comprehensive and/or longitudinal analysis of the type and value
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33 79 of the payment among the oncology specialists.
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38 82 **Word count: 4,255**

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40 84 **Introduction**

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49 85 Cancer has been the leading cause of mortality in Japan since 1981. The government
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52 86 introduced its first Comprehensive 10-year Strategy for Cancer Control (1984-1993),
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55 87 followed by a New 10-year Strategy to Overcome Cancer (1994-2003) and a third
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7 88 Comprehensive 10-year Strategy for Cancer Control in 2014, aimed at boosting cancer
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10 89 research and provide high-quality cancer interventions and services. In 2015, an
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12 90 “Acceleration Plan for Cancer Control” was proposed with three key foci, “prevention”,
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15 91 “treatment/research” and “coexistence with cancer”, with a Basic Plan to Promote
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18 92 Cancer Control Programs being approved in 2017. In 2016, the year our study covered,
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21 93 there were 372,986 cancer deaths in Japan, with malignant neoplasms costing the nation
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24 94 an estimated ¥3.6 trillion [£24.4 billion, €28.9 billion, \$33.1 billion] in medical
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27 95 expenditure. In males, lung cancer was the leading cause of cancerous deaths (52,430)
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30 96 in 2016, followed by gastric cancer (29,854) and colorectal cancer (27,026), while
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33 97 colorectal cancer was the leading cause of cancerous death in females (23,073),
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36 98 followed by lung cancer (21,408) and colorectal cancer (17,405), in the same year.¹
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39 99 The risk factors for cancer are diverse, including tobacco use, infection, obesity,
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42 100 radiation exposure, reproductive and hormonal factors, and other environmental and
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45 101 occupational pollutants and carcinogens.² In case of Japan, primarily with the
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48 102 population ageing, its cancer death is estimated to continuously increase in future.¹
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54 104 For the pharmaceutical industry, medical and therapeutic practice generates substantial
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57 105 income, allowing it to satisfy market demand and exploit various opportunities to
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6 106 expand their own profits.³⁻⁵ From the 1950s, the main business model of the
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9 107 pharmaceutical industry was the production of low-price drugs to treat diseases and
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12 108 conditions that were primarily chronic and prevalent (e.g. hypertension and diabetes).⁶⁻⁸
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15 109 Following advances of drug development against infectious and chronic diseases,
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18 110 cancer became an ever-increasing and major problem, with 17.2 million incidents and
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21 111 213.2 million cancer-associated disability-adjusted life-years (DALY) lost during 1990-
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24 112 2016 worldwide.⁹ The pharmaceutical industry therefore adopted a new business model,
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27 113 discovery and development of anticancer agents that could be sold at extremely high
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30 114 price, but usually for short treatment durations.³⁻⁵ This guaranteed a hefty profit in a
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33 115 short timeframe - provided that the drugs would be prescribed and used - while
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36 116 imposing an extraordinarily high cost on patients and health systems.^{3-5 10} Indeed, a
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39 117 single administration of tisagenlecleucel, a recently-approved chimeric antigen receptor
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42 118 T-cell immunotherapy manufactured by Novartis Pharma, reportedly costs \$475,000.¹¹
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48 120 Physicians remain paramount decision-makers on the demand-side of the
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51 121 pharmaceutical market. Even subtle financial interactions between physicians and a
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54 122 pharmaceutical company are known to affect their prescribing behavior,¹²⁻¹⁷ and could
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57 123 encourage irrational or preferential use of a company's drug. Unsurprisingly, given the
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6 124 cost of anticancer drugs, oncologists have latterly become primary targets for
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9 125 approaches from companies with high-cost anticancer products to sell. Indeed,
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12 126 significant financial relationships between such companies and the authors of the
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15 127 Clinical Practice Guidelines (CPGs) issued by the National Comprehensive Cancer
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18 128 Networks (NCCN) in the United States have been reported.¹⁸ Given these far from ideal
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21 129 circumstances, there has been a growing need for intervention, in the form of policy
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24 130 implementation and education about the implications of these interactions to help
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27 131 protect doctors, patients, institutions and the companies themselves.¹⁴⁻¹⁷ Consequently,
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30 132 medical and governmental facilities worldwide are considering guidelines, self-
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33 133 regulation and legislative checks to help control the relationship between physicians and
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36 134 the pharmaceutical industry, exemplified by the USA's Physician Payments Sunshine
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39 135 Act, enacted in 2010.^{19 20}
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45 137 Although Japan has the world's third largest pharmaceutical market, with annual sales
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48 138 of \$76 billion in 2017,²¹ its overall scale has been declining at approximately 2%
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51 139 annually.²² To maintain sales in these competitive and tightening markets, forceful
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54 140 advertisement of high-price products, namely novel oncology drugs, has become
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57 141 increasingly important for pharmaceutical companies. Indeed, sales of oncology drugs
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6 142 have recently been rising in Japan, exceeding ¥1 trillion [£6.8 billion, €8.0 billion, \$9.2
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9 143 billion] for the first time in 2016.²³ Furthermore, sales are predicted to increase 1.5–fold
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12 144 in the next decade with the increasing application of immunotherapy in clinical
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15 145 practice.²³ It would be reasonable to assume that pharmaceutical companies will
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18 146 increasingly deploy marketing measures and incentives targeting oncology specialists
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21 147 for the immediate and foreseeable future.
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27 149 In Japan, the Japan Pharmaceutical Manufacturers Association (JPMA) covers a
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30 150 majority of companies that manufacture brand name drugs in Japan. Its members
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33 151 accounted for 80.8% of total pharmaceutical sales in Japan in 2015.²⁴ In 2011, the
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36 152 JPMA published transparency guidelines requiring all member companies to disclose all
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39 153 payments for speaking, writing and consulting made to all individuals, specifying their
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42 154 names and affiliations.²⁵ The aim was to improve the transparency of linkages between
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45 155 pharmaceutical companies and physicians, as in the Open Payments Database in the
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48 156 United States.^{19 20} However, the disclosure format, whereby companies involved
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51 157 published the required data on their own individual websites, has differed among and
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54 158 between companies and the aggregated, standardized payment data have not been
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6 159 readily available.²⁶ As a result, an examination of company/physicians links and
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9 160 payments in a meaningful way has proved almost impossible.
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15 162 The aims of the current study were: 1) to understand and evaluate the characteristics and
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18 163 distributions of financial payments made by pharmaceutical companies to oncology
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21 164 specialists: 2) to examine a well-accepted belief that pharmaceutical companies make
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24 165 payments to promote their products; and 3) to elucidate what Japanese oncology
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27 166 specialists are obliged to disclose with respect to any conflicts of interest.
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31 32 33 168 **Methods**

34 35 36 169 *Study setting and participants*

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39 170 The Japan Society of Medical Oncology (JSMO), with over 9154 general members, is
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42 171 the one of the largest professional medical societies in the clinical oncology field in
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45 172 Japan. The JSMO began operating a specialty registration system for members in 2004.
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48 173 This required JSMO members wishing to be certified to meet specific requirements for
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51 174 both oncology care and academic achievement. Only after passing the requisite
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54 175 examination, could they become board-certified oncology specialists with renewed
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6 176 certification of every 5 years. We included all oncology specialists certified by the

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9 177 JSMO as of April 1st, 2016.

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15 179 *Sources of Payment Data*

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18 180 The sources of the payment data were the websites of the 78 pharmaceutical companies

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21 181 involved in this study. These companies publish data of payments made to physicians

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24 182 and other researchers annually under the transparency guidelines of the JPMA. They

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27 183 were categorized into 71 active JPMA members, six affiliated entities of these

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30 184 companies, and one past member. The companies included in this study, plus the

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33 185 starting and ending dates of their payment data, are listed in Supplementary Material 1.

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39 187 We obtained each company's data and organized them into a unified single database.

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42 188 This was done because no data was published as a spreadsheet, so data with character

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45 189 codes were converted into a spreadsheet format and data with no character codes were

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48 190 converted into text files using an Optical Character Reader. Moreover, where data was

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51 191 protected against facsimile or reproduction, we used FullShot10 software (Inbit, CA,

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54 192 USA) to scan photos of the data and converted the data into text files. The accuracy of

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57 193 the re-organized data was confirmed by comparing it with the original data. The

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6 194 database included physicians' names, their main institutional affiliation, payments
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9 195 received, the form of the payments, and the total amount paid. The form of payment
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12 196 was categorized into three types; payment for speaking engagements, payment for
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15 197 writing or publication work, and consulting fees. For the purposes of this study, we
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18 198 converted Japanese yen (¥) to Pound Sterling (£), Euro (€), and US dollars (\$), using the
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21 199 average monthly exchange rate for 2016, namely ¥147.7 per £1, ¥124.5 per €1 and
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24 200 ¥108.8 per US\$1.
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30 202 *Data collection*

33 203 We examined payment data for all oncology specialists included in this study. We
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36 204 extracted their working institutions and regional locations, along with the year of their
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39 205 certification by the JSMO. We further confirmed the accuracy of such information in
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42 206 the year 2016, collating data from institutional websites and other sources. We
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45 207 speculated the cancer specialties (respirology, gastroenterology, hematology, breast,
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48 208 etc.) of all oncologists who received total payment of ¥1 million [£6.8 thousand, €8.0
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51 209 thousand, \$9.2 thousand] or above from the included pharmaceutical companies, using
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54 210 data from institutional websites and other sources as well. In general, ¥1 million is
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57 211 approximately 25% of the median annual income of a Japanese citizen.²⁷ In addition, we
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6 212 sought to examine any prevailing COI policy from the JSMO website that could apply

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9 213 to oncologists.

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15 215 *Data analysis*

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18 216 To examine the characteristics and distributions of payments, we performed descriptive

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21 217 analyses of the data on an individual oncology specialist and pharmaceutical company

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24 218 basis. We then summarized the characteristics of oncology specialists according to the

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27 219 total monetary value of the payment they received, dividing the patients into the three

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30 220 groups; ¥1 million or above (High-payment Group); ¥1 – 1 million (Low-payment

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33 221 Group), and ¥0 (No-payment Group).

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40 223 Using a multivariate negative binomial regression model, we subsequently examined

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43 224 possible factors associated with the monetary value of the payment to the individual

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46 225 oncologists, using institutional place of work, regional working locations, and year of

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49 226 experience after board certification as covariates. The payment data was rounded off as

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52 227 a unit of ¥1 million. Further, to assess the effects of the cancer specialty on the value of

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55 228 the payment, using a zero-truncated negative binomial model, we repeated the analysis

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58 229 in High-payment Group. In addition, for Low-payment and No-payment Groups we

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6 230 examined possible factors associated with the monetary value of the payment to the
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9 231 individual oncologists, using the same model adopted as for the overall population. For
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12 232 this analysis, the payment data was rounded off as a unit of ¥100,000 [£677, €803,
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15 233 \$919]. Second, we created a Sankey diagram among the specialists in this cohort to
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18 234 illustrate the distribution of the payment to each specialty on an individual company
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21 235 basis. The Sankey diagram is a flow diagram, where band width proportionally
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24 236 represents the flow quantity.²⁸ Payment values from individual companies, according to
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27 237 cancer specialty, are depicted in the bands in the diagram, width being proportional to
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30 238 the total amount of the payment. In addition, to see whether the payment was linked to
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33 239 any specific oncology drugs, we examined such drugs with annual Japanese domestic
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36 240 sales of ¥5 billion [£33.9 million, €40.2 million, \$46.0 million] or above in the fiscal
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39 241 year of 2016, and if each drug was covered under the Japanese National Health
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42 242 Insurance scheme in specific oncology subspecialty by the end of the same year (March
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45 243 31, 2017). We further examined newly-approved drugs and drugs with an added
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48 244 indication during the fiscal years of 2015 and 2016 (April 1, 2015 to March 31, 2017).

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55 246 *Human subject involvement*
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6 247 The present study is a retrospective analysis of existing databases and public domain
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9 248 information. No patients or any other individuals were other than unnamed oncology
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12 249 specialists were included in the study.
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18 251 **Results**

21 252 The JSMO had over 9000 members at the time the study was undertaken, with 1081
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24 253 physicians having been board certified as oncology specialists. We excluded one
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27 254 oncologist whose professional affiliation we were unable to confirm, and he did not
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30 255 receive any payment from the pharmaceutical companies. Thus, we included a total of
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33 256 1,080 specialist oncologists in our analyses.
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39 258 Table 1 summarizes the details of certified oncologists and payments from Japanese
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42 259 pharmaceutical firms. Of the 1080 selected certified oncology specialists, 442 (40.9%),
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45 260 183 (16.9%), and 455 (42.1%) worked for university hospitals, cancer hospitals, and
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48 261 other institutions, respectively. The number of specialists certified by the JSMO from
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51 262 2004 onwards was largest in 2013 (143 [13.2%]), the number of new certifications
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54 263 displaying a downward trend during the subsequent years (2014 [98, 9.1%], 2015 [85,
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57 264 7.9%], and 2016 [76, 7.0%]).
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266 A total of 7325 payments were recorded, the total monetary value being ¥585,453,314

267 [£3,963,800, €4,702,436, \$5,381,005]. Of this total, ¥467,802,690 [£3,167,249,

268 €3,757,451, \$4,299,657] was for speaking engagements, ¥94,682,807 [£641,048,

269 €760,504, \$870,246] was for consulting services, and ¥22,266,186 [£150,753,

270 €178,845, \$204,652] was paid for writing work. The median monetary value and count

271 of an individual payment was ¥120,016 [£813, €964, \$1,103]. (interquartile range (IQR)

272 ¥0 – ¥449,378 [£3,043, € 3,609, \$4,130] and 2 (IQR 0–7), respectively.

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274 Of the 1080 individuals, 763 (70.6%) received at least one payment. Furthermore, 142

275 (13.1%) received payments totaling \geq ¥1 million, while 19 (1.8%) received \geq ¥5 million

276 [£33.9 thousand, €40.2 thousand, \$46.0 thousand]. Two individuals (0.2%) received

277 \geq ¥10 million [£67.7 thousand, €80.3 thousand, \$91.9 thousand].

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279 Table 2 summarizes the monetary values and counts of payments made by the 78

280 pharmaceutical companies. In total, 59 (75.6%) companies made at least one payment to

281 oncology specialists. The Chugai Pharmaceutical Co. Ltd., a subsidiary of F. Hoffmann-

282 La Roche Ltd, made the largest accumulated payment of ¥103,830,493 [£702,982, €

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6 283 833,980, \$954,324]. The median monetary value and count among the 78 companies
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9 284 was ¥645,947 [£4,373, €5,188, \$5,937] (IQR ¥33,410 [£226, €268, \$307] – ¥5,196,201
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12 285 [£35,181, €41,737, \$47,759] and 10 (IQR 1 – 71), respectively.
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18 287 Table 3 ranks the oncology specialists according to the monetary value of the payments
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21 288 they received. In High-payment Group, 52.8% (75) of the oncologists worked for
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24 289 university hospitals, while 28.2% (40) worked for cancer hospitals: these figures were
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27 290 larger than those seen in the other two groups. Further, while only 19.7% (28) of the
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30 291 specialists in High-payment Group were certified during the previous five years (2012
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33 292 to 2016), 49.4% (307) and 60.3% (191) of Low-payment and No-payment Groups
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36 293 respectively were certified during these five years. The top three cancer specialties
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39 294 attracting payments were respirology (53 [37.3%]), gastroenterology (32 [22.5%]), and
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42 295 hematology (29 [20.4%]).
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48 297 In Group A, the total monetary value paid and number of payments were ¥418,345,258
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51 298 [£2,832,398, €3,360,203, \$3,845,085] and 4466, respectively, accounting for 71.5% and
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54 299 61.0% of the totals, with the largest three specialties of respirology (¥166,220,775
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57 300 [£1,125,395, €1,335,107, \$1,527,764], 39.7%), gastroenterology (¥91,319,282
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6 301 [£618,275.00, €733,488, \$839,332], 21.8%) and hematology (¥84,186,048 [£569,980,
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9 302 €676,193, \$773,769], 20.1%).

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15 304 Table 4 displays findings of the multivariate regression analyses for the monetary value
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18 305 of payments. Oncologists with longer experience after board certification were
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21 306 significantly more likely to receive larger payments compared with those with shorter
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24 307 experience after certification (relative monetary value (RMV)=1.32, 95% CI=1.26 –
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27 308 1.39). Those working for university hospitals (RMV=2.98, 95% CI=2.11 – 4.21) and
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30 309 those working for cancer hospitals (RMV=3.19, 95% CI=2.14 – 4.76) also tended to
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33 310 receive higher payments compared with those working for other types of institutions.

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36 311 The trends observed in Group A were not reflected in Groups B and C: in these groups,
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39 312 there were no significant differences in the monetary value of the payment depending
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42 313 on the type of affiliation. Those working in respirology were likely to receive higher
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45 314 payments compared with all others, although this trend was not statistically significant.

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51 316 Figure 1 displays payment distributions to each cancer specialty on an individual
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54 317 company basis. Details of the payments are provided in Supplementary Material 2.

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57 318 Further, in Supplementary Material 3, we summarize the list of oncology drugs with
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6 319 Japanese domestic sales of ¥5 billion or more. Chugai Pharmaceutical Co., Ltd. made
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9 320 the largest specialty payment of ¥74,376,669 [£503,566, €597,403, \$683,609] and the
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12 321 top four specialties were respiratory (¥24,545,685 [£166,186, €197,154, \$225,604],
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15 322 33.0%), gastroenterology (¥23,656,984 [£160,169, €190,016, \$217,436], 31.8%),
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18 323 hematology (¥14,432,072 [£97,712, €115,920, \$132,648], 19.4%), and breast cancer
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21 324 (¥8,958,305 [£60,652, €71,954, \$82,337], 12.0%). The Chugai company manufactured
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24 325 eight oncology drugs with annual sales of ¥5 billion or more (Supplementary Material
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27 326 3), and three, three, one, and five drugs were respectively covered under the National
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30 327 Health Insurance scheme for the field of respiratory, gastroenterology, hematology and
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33 328 breast. Nivolumab, manufactured by the Ono Pharmaceutical Co., Ltd., mainly used in
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36 329 lung cancer and melanoma, had the largest domestic sales in 2016 (¥103.9 billion
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39 330 [£703.5 million, €834.5 million, \$955.0 million]). The total monetary value of the
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42 331 company's payments was ¥35,035,323 [£237,206, € 281,408, \$322,016], (representing
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45 332 fourth place in the payment table), of which ¥22,619,251 [£153,143, €181,681,
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47
48 333 \$207,898], (64.6%) was specifically distributed for respiratory work. All of the top
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51 334 eight companies with regard to the monetary value of the payments (Supplementary
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54 335 Material 2) had at least one drug which was newly approved that with an added
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57 336 indication under the National Health Insurance scheme in the fiscal years of 2015 and
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6 337 2016. While AstraZeneca plc had no oncology drugs with Japanese domestic sales of at
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9 338 least ¥5 billion (Supplementary Material 3), vandetanib and osimertinib was newly
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12 339 approved for thyroid cancer in September 28, 2015 and non-small cell lung cancer in
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15 340 March 28, 2016, respectively (Supplementary Material 4). The total monetary value of
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17
18 341 the company's payments was second, accounting for ¥42,544,963 [£288,050, €341,727,
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21 342 \$391,038]. Of the total, 86.0% (¥36,577,758 [£247,649, €293,797, \$336,193]) was
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24 343 specifically distributed for respirology work.
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30 345 The JSMO has guideline on the COI disclosure for its members. Its members are
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33 346 required to disclose their COIs associated with publications and other research
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36 347 presentations. Further, executive board members, auditors, and other high-class
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39 348 members, as well as presidents and vice-presidents of conferences and committee
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42 349 members under the JSMO are required to disclose their COIs associated with their
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45 350 works and positions. These include, with respect to any for-profit organization,
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48 351 reporting any 1) Position as an officer or advisor, 2) Stock ownership, 3) Patent
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51 352 royalties or licensing fees, 4) Honoraria (e.g. lecture fees), 5) Fees paid for any writing
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54 353 or publication work, 6) Receipt of research funding, 7) Advisory fees or financial
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57 354 remuneration in exchange for testimony, 8) Acceptance of researchers from any for-
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6 355 profit enterprise, 9) Endowed chairs offered, and 10) Remuneration (travel, gifts, or
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9 356 other in-kind payments not directly related to research). However, there are no specific
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12 357 rules specifically referring to oncology specialists.
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18 359 **Discussion**

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21 360 In 2016, approximately ¥600 million [£4.1 million, €4.8 million, \$5.5 million] was paid
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24 361 by Japanese pharmaceutical companies to 763 (70.6%) certified oncology specialists.
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27 362 Payments appeared to be concentrated on specific targets, notably experienced
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30 363 oncologists working for university hospitals and cancer hospitals.
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36 365 The proportion of oncologists receiving payments was larger compared with general
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39 366 physicians in the US (48.0%)²⁹ and Japan (33.3%).³⁰ However, the proportion was
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42 367 slightly smaller than that of NCCN oncology CPG authors in the US (86.4%).¹⁸
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45 368 Although the mean value of payments in our study was approximately half of that of the
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48 369 CPG authors (\$4,888 [data not shown] vs.\$10,011), a simple comparison is not valid, as
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51 370 our analysis did not include payments related to meals, transportation and
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54 371 accommodation, stock ownership, investment interest, or payments from medical device
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57 372 companies.²⁹ The CPG authors strongly influence oncology practice, both in the US and
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6 373 internationally,³¹ by recommending treatment algorithms. They thus become prime
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9 374 targets for pharmaceutical companies selling anticancer products. It is reasonable to
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12 375 assume that Japanese pharmaceutical companies with similar anticancer interests would
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15 376 target oncology specialists in an attempt to boost the sales and use of their specific
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18 377 products.

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24 379 We observed a large disparity in payments to specialists. Those receiving ¥1 million or
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27 380 more accounted for 13.1% of all oncologists studied but received 71.5% of the total
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30 381 paid. Oncologists working for university hospitals and those working for cancer
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33 382 hospitals similarly received large value payments. In Japan, cancer centers are generally
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36 383 more likely to treat more cancer patients compared to university hospitals. Indeed,
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39 384 cancer centers top the nationwide ratings for treatments of most of the common cancers,
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42 385 including lung, colon, gastric, and breast cancer.³² In contrast, university hospitals are
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45 386 regarded as symbols of academic excellence and authority, and medical school
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48 387 professors traditionally have a strong influence on both physicians and medical practice
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51 388 in their field of expertise. They are more influential in setting treatment protocols which
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54 389 are usually followed without question by less senior medical staff nationwide. Thus, our
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57 390 findings suggest that Japanese pharmaceutical companies have placed emphasis on
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6 391 expertise and authority, as well as clinical experience, in the selection of targets for their
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9 392 promotional activities.
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15 394 We found that respirology attracted the greatest financial outlay. In Japan, lung cancer
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18 395 is of primary concern at present, covering a large patient volume and consequently
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21 396 attracting multiple novel oncology drugs, such as alectinib (Chugai Pharmaceutical Co.,
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24 397 Ltd., [2014]), nivolumab (Ono Pharmaceutical Co., Ltd, [approved 2015]), afatinib
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27 398 (Nippon Boehringer Ingelheim Co., Ltd., [2016]), certinib (Novartis Pharma K.K.,
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30 399 [2016]), osimertinib (AstraZeneca plc, [2016]), pembrolizumab (MSD K.K., [2016]),
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33 400 ramcirumab (Eli Lilly Japan K.K., [2016]), all for non-small cell lung cancer
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36 401 (Supplementary Materials 3 & 4). As such, for the pharmaceutical companies, this field
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39 402 is a critical yet highly competitive target in any strategy to maximize the cost-
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42 403 effectiveness of their promotional endeavors.
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48 405 The examples of Chugai Pharmaceutical and Ono Pharmaceutical chiefly support the
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51 406 belief that there is an association between the value and destination of payments
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54 407 dependent on the products the companies in question manufacture. In contrast, the
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57 408 example of AstraZeneca confirms the idea that that funds were mainly allocated to
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6 409 promote their novel product: osimertinib was approved for non-small cell lung cancer in
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9 410 March 2016. Indeed, 86% of the company's payment was allocated to respirology.
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15 412 As we have demonstrated, there is an emphatic financial relationship between
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18 413 pharmaceutical companies and oncologists. It is true that the receipt of the
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21 414 abovementioned payments in Japan is not illegal, as they are supposedly given as
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24 415 remuneration for work undertaken or services rendered. However, we believe that there
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27 416 is an ethical problem inherent in such relationships, given that this practice could have
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30 417 been instigated and developed to possibly end up expanding the profit of
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33 418 pharmaceutical companies, rather than promoting the health and well-being of patients.
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36 419 Indeed, even a subtle but reputable financial relationship with the industry, such as
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39 420 collaborating in a field trial, could bias a physician's prescription patterns in a manner
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42 421 that benefits the companies.¹²⁻¹⁷ Oncologists in Japan handle extraordinary and very
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45 422 potent life-saving drugs, and have a degree of autonomy in their prescribing actions.
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48 423 Their decisions substantially influence the treatment and outcome for their patients, as
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51 424 well as having significant economic impact due to the high cost of anticancer
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54 425 medications.³⁻⁵ It would therefore appear sensible to have rigorous regulations in place
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57 426 which necessitate the open and accessible reporting of any financial dealings between
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6 427 physicians and pharmaceutical companies, so as to avoid any potential nefarious or
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9 428 underhand behavior or undue pressure on physicians to alter their usual treatment
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12 429 practices. Indeed, it is possible that these highly-questionable arrangements may have
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15 430 contributed to the multiple cases of scientific misconduct that have recently been
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18 431 reported in Japan. The most infamous case was when employee misconduct was
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21 432 discovered in a series of clinical trials for Valsartan, an antihypertensive medication
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24 433 manufactured by Novartis Pharma, leading to a retraction of the associated academic
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27 434 papers.^{33 34} A breast cancer clinical trial (CREATE-X trial) with a questionable
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30 435 pharmaceutical payment has also been identified.^{35 36}
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36 437 To prevent similar cases in future, we call for the implementation of a transparent,
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39 438 independent mechanism that would enable a comprehensive assessment of any and all
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42 439 payments being made by any pharmaceutical company to any individual physician or,
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45 440 for that matter, medical institution where the company's products may be used - and not
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48 441 just with respect to oncology. This has to be mandatory and legally-binding on the side
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51 442 of both the company and physician. New schemes along these lines, such as the US's
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54 443 Open Payments Database, may prove successful but it is too soon to know.³⁷ The
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57 444 Disclosure UK mechanism may not prove to be so effective as it is voluntary.
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6 445 Additionally, given that such mechanisms allow for direct comparison between what is
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9 446 allegedly paid and what is allegedly received, it will necessitate a fair, equitable and
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12 447 timely mechanism for dispute settlement, probably involving the use of third parties.³⁶
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18 449 **Concluding remarks**
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21 450 Japanese certified oncologists receive financial payments directly from pharmaceutical
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24 451 companies, usually from those active in the specialist field of the physician in question.
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27 452 This raises several queries with regard to ethical, medical, corruption and possibly legal
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30 453 issues. The value and specialty targets of the payments varied substantially, which also
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33 454 raises yet more questions as to why. We believe that the lessons learned from our
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36 455 analyses should be shared among the global medical community to help put in place
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39 456 safeguards to prevent undue and unethical inducements from the pharmaceutical
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42 457 industry and to help protect physicians from outside influences. It is essential to
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45 458 establish a robust, comprehensive and legally-binding system for identifying and
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48 459 avoiding any and all potential conflicts of interest, of any nature, involving physicians
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51 460 or other medical professionals, both in Japan and internationally. While it is too early to
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54 461 evaluate whether similar systems, such as the US-based Open Payments Database, will
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57 462 be truly effective, financial transparency is a fundamental component in illustrating that
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6 463 there is an open, honest and ethically correct relationship between pharmaceutical
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9 464 companies and physicians. A more comprehensive study is planned, to include all
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12 465 Japanese oncologists, to try and confirm our findings and to help identify the best way
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15 466 forward to ensure that COI are avoided and so that physicians and pharmaceutical
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18 467 companies can work harmoniously and synergistically to provide Japan with the best
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21 468 cancer prophylaxis, treatment and cure possible.
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27 470 **Study Limitations**

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30 471 Several limitations in this preliminary study should be acknowledged. First, there could
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33 472 be measurement errors in the affiliations and subspecialties of the included speculates,
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36 473 as we speculated the accuracy of these data in the study year (2016), mainly using the
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39 474 affiliation websites and other data sources on the Internet. Second, there might be minor
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42 475 measurement errors in the payment database as well. Most of the pharmaceutical
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45 476 companies involved did not disclose their payment data in a uniform or readily available
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48 477 format. As a result, we manually entered all the payment data from a variety of formats,
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51 478 and, despite repeated and careful review, the database may include minor errors. Third,
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54 479 the present research analyzed only limited payment types. Currently, Japanese
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57 480 pharmaceutical companies do not disclose payment data for stock interest, loyalties, and
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6 481 costs of meals, transportation, and accommodation. As, unlike the pharmaceutical
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9 482 companies, the JMSO and other similar academic and learned societies in Japan, where
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12 483 such data may be registered, refuse to open their databases to public scrutiny, we were
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15 484 not able to consider these data in this study. Fourth, most of the pharmaceutical
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18 485 companies only publish single year data so we could only consider payments made in
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21 486 2016. To understand temporal trends and the extent and distribution of pharmaceutical
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24 487 company payments, a continuous assessment of the payment data is warranted in future.
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27 488

30 489 **Ethics approval**

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33 490 This study was approved by the Institutional Review Board of the Medical Governance
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36 491 Research Institute (MEGRI) on 16th May 2018.
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39 492

42 493 **Author contributors**

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45 494 AO acquired and controlled all sources of data, and oversaw all data analyses.
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48 495 AO, HS, YO, TS, YShim, YSom, AT, and TT were involved in the study concept and
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51 496 design.
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54 497 AO, HS, YO, TS, YShim, YSom, AT, and TT were involved in the analysis,
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57 498 interpretation of results and formation of conclusions.
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6 499 A.O. drafted the manuscript.
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28
29
30 507 either the design of the study, the work carried out or the interpretation of the study
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33 508 findings.
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45 512 Chronicle - made no contribution whatsoever to either the design of the study, the work
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48 513 carried out or the interpretation of the study findings.
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54 515 **Conflict of Interest statement**
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6 516 AO and TT receive personal fees from Medical Network Systems (MNES Inc.); HS has
7
8
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15 519 interests.
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18 520

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25
26
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33 525 **Data availability statement**

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36 526 The datasets analyzed during the current study are available from the corresponding
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39 527 author on reasonable request.
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6 **530 Figure legends**
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9 **531 Figure 1.** Distribution of payments to each subspecialty on an individual company

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12 **532** basis. The companies and specialties are sorted in descending order with regard to

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15 **533** payment value (proportionally expressed in the box height and band width in Figure 1).

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18 **534** Band color represents the payment destination specialties. Due to space limitations,

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21 **535** names of companies with payment values of less than ¥10 million (£67.7 thousand,

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24 **536** €80.3 thousand, \$91.9 thousand) have been omitted.

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27 **537**

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671 **Table 1. Characteristics of oncology specialists and pharmaceutical payment**
 672 **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 range)	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)

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

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

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676 **Table 2. Companies making a payment to oncology specialists and monetary value**
 677 **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

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6	AbbVie GK,	2,082,626 [14,100]	17
7	Shionogi & Co., Ltd.	1,948,968 [13,195]	28
8			
9	Kyorin Pharmaceutical Co., Ltd.	1,918,033 [12,986]	34
10			
11	Tsumura & Co.	1,681,688 [11,386]	21
12			
13	Meiji Seika Pharma Co., Ltd.	1,289,000 [8,727]	24
14	Terumo Corporation	1,214,840 [8,225]	16
15			
16	Kissei Pharmaceutical Co., Ltd.	1,124,840 [7,616]	9
17	Zeria Pharmaceutical Co., Ltd.	946,645 [6,409]	12
18			
19	Mitsubishi Tanabe Pharma Corporation	935,508 [6,334]	17
20			
21	EA Pharma Co., Ltd.	783,712 [5,306]	17
22			
23	Taisho Toyama Pharmaceutical Co., Ltd.	701,631 [4,750]	11
24	Kowa Company, Ltd.	590,262 [3,996]	5
25			
26	Hisamitsu Pharmaceutical Co., Inc.	539,030 [3,649]	11
27	Novo Nordisk Pharma Ltd.	474,360 [3,212]	8
28			
29	Sanwa Kagaku Kenkyusho Co., Ltd.	445,480 [3,016]	4
30			
31	Aska Pharmaceutical Co., Ltd.	423,206 [2,865]	6
32			
33	Shire Japan K.K	367,521 [2,488]	5
34	Nihon Pharmaceutical Co., Ltd.	311,836 [2,111]	8
35			
36	Nippon Chemiphar Co., Ltd.	278,425 [1,885]	3
37	Ayumi Pharmaceutical Corporation	226,864 [1,536]	3
38			
39	Mylan Seiyaku Ltd.	206,240 [1,396]	4
40			
41	Kracie Holdings, Ltd.	134,056 [908]	2
42			
43	GlaxoSmithKline K.K.	111,370 [754]	2
44	Minophagen Pharmaceutical Co.	110,440 [748]	2
45			
46	Maruho Co., Ltd.	103,120 [698]	1
47	Torii Pharmaceutical Co., Ltd.	102,260 [692]	2
48			
49	EN Otsuka Pharmaceutical Co., Ltd.	89,096 [603]	2
50			
51	Kaken Pharmaceutical Co., Ltd.	77,959 [528]	1
52			
53	Toray Industries, Inc.	77,080 [522]	1
54	Santen Pharmaceutical Co., Ltd.	51,560 [349]	1
55			
56	Toyama Chemical Co., Ltd.	33,410 [226]	1
57			
58	Bee Brand Medico Dental. Co., Ltd.	0 [0]	0
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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

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

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681 **Table 3. Characteristics of oncology specialists and pharmaceutical company payments received in 2016, according to the**
 682 **monetary value of the payment**
 683

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)
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)

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4	2008	19 (13.4)	38 (6.1)	14 (4.4)
5	2009	19 (13.4)	56 (9.0)	23 (7.3)
6	2010	23 (16.2)	80 (12.9)	30 (9.5)
7	2011	16 (11.3)	73 (11.8)	41 (12.9)
8	2012	9 (6.3)	72 (11.6)	43 (13.6)
9	2013	9 (6.3)	79 (12.7)	55 (17.4)
10	2014	5 (3.5)	65 (10.5)	28 (8.8)
11	2015	2 (1.4)	51 (8.2)	32 (10.1)
12	2016	3 (2.1)	40 (6.4)	33 (10.4)

16 Subspecialty of oncologists (N, %)

17				
18	Respirology	53 (37.3)		
19	Gastroenterology	32 (22.5)		
20	Hematology	29 (20.4)		
21	Breast	16 (11.3)		
22	Head and neck	3 (2.1)		
23	Urology	1 (0.7)		
24	Other	8 (5.6)		

28 Characteristics of pharmaceutical payment

29				
30	Total payment			
31	Total value of payment (¥ [£])	418,345,258 [2,832,398]	167,108,056 [1,131,402]	
32	Total count of payment	4,466	2,859	
33				
34	Type of payment (¥ [£], %)			
35	Speaking	327,075,925 [2,214,461], 78.2	140,726,765 [952,788], 84.2	
36	Consulting	73,870,218 [500,137], 17.7	20,812,589 [140,911], 12.5	
37	Writing	17,053,868 [115,463], 4.1	5,212,318 [35,290], 3.1	

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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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686 **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)	

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687 † 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

688 “other” category; CI=Confidence interval; * <0.05, ** <0.01, *** <0.001

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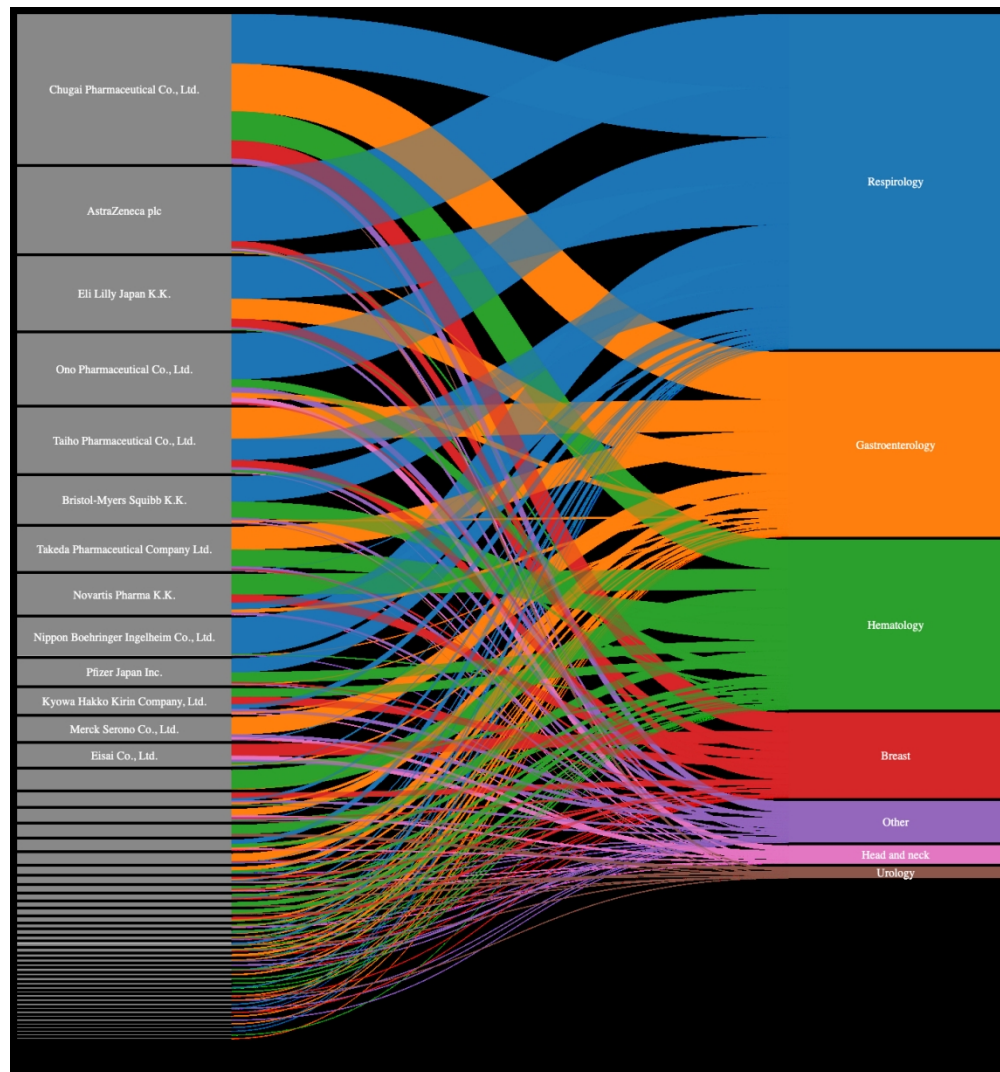


Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band color represents the payment destination specialties.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

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4	Japan Tobacco Inc. ^d	Not available	Not available
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6	Kaken Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
7			
8	Kissei Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
9			
10	Kowa Company, Ltd.	April 1, 2016	March 31, 2017
11			
12	Kracie Holdings, Ltd.	January 1, 2016	December 31, 2016
13			
14	Kyorin Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
15			
16	Kyoto Pharmaceutical Industries, Ltd.	June 1, 2016	May 31, 2017
17			
18	Kyowa Hakko Kirin Company, Ltd.	January 1, 2016	December 31, 2016
19			
20	Maruho Co., Ltd.	October 1, 2016	September 30, 2017
21			
22	Maruishi Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
23			
24	Meiji Seika Pharma Co., Ltd.	April 1, 2016	March 31, 2017
25			
26	Merck Serono Co., Ltd.	January 1, 2016	December 31, 2016
27			
28	Minophagen Pharmaceutical Co.	April 1, 2016	March 31, 2017
29			
30	Mitsubishi Tanabe Pharma Corporation	April 1, 2016	March 31, 2017
31			
32	Mochida Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
33			
34	MSD K.K.	January 1, 2016	December 31, 2016
35			
36	Mylan Seiyaku Ltd.	January 1, 2016	December 31, 2016
37			
38	Nihon Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
39			
40	Nippon Boehringer Ingelheim Co., Ltd.	January 1, 2016	December 31, 2016
41			
42	Nippon Chemiphar Co., Ltd.	January 1, 2016	December 31, 2016
43			
44	Nippon Kayaku Co., Ltd.	April 1, 2016	March 31, 2017
45			
46	Nippon Shinyaku Co., Ltd.	April 1, 2016	March 31, 2017
47			
48	Nippon Zoki Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
49			
50	Novartis Pharma K.K.	January 1, 2016	December 31, 2016
51			
52	Novo Nordisk Pharma Ltd.	January 1, 2016	December 31, 2016
53			
54	Ono Pharmaceutical Co., Ltd.	April 1, 2016	March 31, 2017
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56	Otsuka Holdings Co., Ltd. ^e	January 1, 2016	December 31, 2016
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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]

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5	Pfizer Japan Inc.	6,683,175	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
6		[45,248]							[88,349]
7									
8	Kyowa Hakko Kirin Company, Ltd.	2,338,770	902,097 [6,108]	3,975,910 [27,496]	3,669,644	111,370	0 [0]	1,470,089	12,467,880
9		[15,835]			[24,845]	[754]		[9,953]	[84,414]
10									
11	Merck Serono Co., Ltd.	334,110 [2,262]	8,397,065	0 [0]	33,411 [226]	1,258,481	0 [0]	1,369,851	11,392,918
12			[56,852]			[8,521]		[9,275]	[77,136]
13									
14	Eisai Co., Ltd.	445,480 [3,016]	523,439 [3,544]	1,180,522 [8,164]	5,791,243	1,948,977	0 [0]	1,380,988	11,270,649
15					[39,209]	[13,196]		[9,350]	[76,308]
16									
17	Celgene Corporation	0 [0]	103,120 [698]	9,376,553 [64,845]	0 [0]	0 [0]	0 [0]	0 [0]	9,479,673
18									[64,182]
19									
20	Daiichi Sankyo Company, Limited.	1,180,527 [7,993]	915,086 [6,196]	222,740 [1,540]	2,615,204	0 [0]	389,796	973,096 [6,588]	6,296,449
21					[17,706]		[2,639]		[42,630]
22									
23	Bayer Yakuhin, Ltd.	77,959 [528]	3,164,949	412,069 [2,850]	701,634 [4,750]	863,118	278,425	612,535 [4,147]	6,110,689
24			[21,428]			[5,844]	[1,885]		[41,372]
25									
26	Panssen Pharmaceutical K.K.	0 [0]	0 [0]	4,387,980 [30,346]	0 [0]	0 [0]	1,252,917	0 [0]	5,640,897
27							[8,483]		[38,192]
28									
29	MSD K.K.	2,013,013	545,715 [3,695]	1,748,510 [12,092]	278,425 [1,885]	529,009	0 [0]	0 [0]	5,114,672
30		[13,629]				[3,582]			[34,629]
31									
32	Yakult Honsha Company, Limited.	288,740 [1,955]	3,764,259	0 [0]	381,548 [2,583]	0 [0]	0 [0]	381,548 [2,583]	4,816,095
33			[25,486]						[32,607]
34									
35	Sumitomo Dainippon Pharma Co., Ltd.	278,425 [1,885]	1,626,004	1,069,152 [7,394]	0 [0]	0 [0]	0 [0]	77,959 [528]	3,051,540
36			[11,009]						[20,660]
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5	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] [19,329]	2,854,900 [15,386]
6									
7									
8	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]
9									
10									
11	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]
12									
13									
14	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]
15									
16									
17	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]
18									
19									
20	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]
21									
22									
23	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]
24									
25	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]
26									
27	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]
28									
29									
30	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]
31									
32	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]
33									
34	Isumura & Co.	0 [0]	779,590 [5,278]	55,685 [385]	55,685 [377]	0 [0]	0 [0]	0 [0]	890,960 [6,032]
35									
36	Terumo Corporation	110,440 [748]	430,716 [2,916]	0 [0]	0 [0]	0 [0]	0 [0]	110,440 [748]	651,596 [4,412]
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5	Kowa Company, Ltd.	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	556,851 [3,770]	556,851 [3,770]
6									
7	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]
8									
9	Zeria Pharmaceutical Co., Ltd.	0 [0]	445,480 [3,016]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	445,480 [3,016]
10									
11	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]
12									
13	Novo Nordisk Pharma Ltd.	0 [0]	0 [0]	360,925 [2,496]	0 [0]	0 [0]	0 [0]	0 [0]	360,925 [2,444]
14									
15	Faisho 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]
16									
17									
18	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]
19									
20	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]
21									
22	Ayumi Pharmaceutical Corporation	226,864 [1,536]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	226,864 [1,536]
23									
24	Kissei Pharmaceutical Co., Ltd.	111,370 [754]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]	222,740 [1,508]
25									
26	Shire Japan K.K.	0 [0]	0 [0]	222,740 [1,540]	0 [0]	0 [0]	0 [0]	0 [0]	222,740 [1,508]
27									
28									
29	Peijin Pharma Limited.	190,000 [1,286]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	190,000 [1,286]
30									
31	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]
32									
33	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]
34									
35	EA Pharma Co., Ltd.	0 [0]	154,680 [1,047]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	154,680 [1,047]
36									
37	Shire Japan K.K.	0 [0]	0 [0]	111,370 [770]	0 [0]	0 [0]	0 [0]	0 [0]	111,370 [754]
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5	Kracie Holdings, Ltd.	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]	103,120 [698]
6									
7	Maruho Co., Ltd.	0 [0]	103,120 [698]	0 [0]	0 [0]	0 [0]	0 [0]	103,120 [698]	
8									
9	Mitsubishi Tanabe Pharma Corporation	77,959 [528]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959 [528]	
10									
11	GlaxoSmithKline K.K.	55,685 [377]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	55,685 [377]	
12									
13	Nihon Pharmaceutical Co., Ltd.	0 [0]	0 [0]	55,685 [385]	0 [0]	0 [0]	0 [0]	55,685 [377]	
14									
15	EN Otsuka Pharmaceutical Co., Ltd.	0 [0]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	33,411 [226]	
16									
17		166,220,775	91,319,282	84,186,048	42,090,455	8,689,962	5,527,458	20,311,278	418,345,258
18	All	[1,125,395]	[618,275]	[582,200]	[284,973]	[58,835]	[37,424]	[137,517]	[2,832,398]
19									

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

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5	Nippon Boehringer Ingelheim Co., Ltd.	Afatinib	8.7	58.9	Yes	No	No	No	No	No	No
6											
7	Novartis International AG	Imatinib	27.5	186.2	No	Yes	Yes	No	No	No	No
8											
9	Novartis International AG	Nilotinib	20.7	140.1	No	No	Yes	No	No	No	No
10											
11	Novartis International AG	Everolimus	15.1 [†]	102.2 [†]	Yes	Yes	No	Yes	Yes	No	No
12											
13	Ono Pharmaceutical Co., Ltd.	Nivolumab	103.9	703.5	Yes	No	Yes	No	Yes	Yes	Yes
14											
15	Taiho Pharmaceutical Co., Ltd.	Tegafur/Gimeracil/Oteracil	26.9	182.1	Yes	Yes	No	Yes	No	Yes	No
16											
17	Taiho Pharmaceutical Co., Ltd.	nab-Paclitaxel	20.7	140.1	Yes	Yes	No	Yes	No	No	No
18											
19	Taiho Pharmaceutical Co., Ltd.	Calcium Folate	9.7	65.7	No	Yes	No	No	No	No	No
20											
21	Taiho Pharmaceutical Co., Ltd.	Tegafur, Uracil	6.5	44.0	Yes	Yes	No	Yes	Yes	Yes	Yes
22											
23	Takeda Pharmaceutical Co., Ltd.	Leuprorelin	48.6 [†]	329 [†]	No	No	No	Yes	Yes	No	No
24											
25	Takeda Pharmaceutical Co., Ltd.	Panitumumab	18.8	127.3	No	Yes	No	No	No	No	No
26											
27											
28	Yakult Honsha Co., Ltd.	Oxaliplatin	18.4	124.6	No	Yes	No	No	No	No	No
29											

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

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5	Eisai Co., Ltd.	Eribulin	February 29, 2016	Added indication	Sarcoma
6					
7	Eli Lilly Japan K.K.	Ramucirumab	May 23, 2016	Added indication	Colorectal cancer
8					
9	Eli Lilly Japan K.K.	Ramucirumab	June 20, 2016	Added indication	Non-small cell lung cancer
10					
11	GlaxoSmithKline K.K.	Lapatinib	November 20, 2015	Added indication	Breast cancer
12					
13	Janssen Pharmaceutical K.K.	Ibrutinib	March 28, 2016	New approval	Chronic lymphocytic leukemia
14					
15	Janssen Pharmaceutical K.K.	Bortezomib	June 26, 2015	Added indication	Mantle cell lymphoma
16					
17	Janssen Pharmaceutical K.K.	ibrutinib	December 2, 2016	Added indication	Mantle cell lymphoma
18					
19					
20	Meiji Seika Pharma Co., Ltd.	Talaporfin	May 26, 2015	Added indication	Esophageal cancer
21					
22	Minophagen Pharmaceutical Co.	Bexarotene	January 22, 2016	New approval	Cutaneous T cell lymphoma
23					
24	MSD K.K.	Peginterferon Alfa-2b	May 26, 2015	Added indication	Melanoma
25					
26	MSD K.K.	Pembrolizumab	September 28, 2016	New approval	Melanoma
27					
28	MSD K.K.	Pembrolizumab	December 19, 2016	Added indication	Non-small cell lung cancer
29					
30					
31	Mylan Seiyaku Ltd.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
32					
33	Nippon Kayaku Co., Ltd.	Paclitaxel	September 24, 2015	Added indication	Gastric cancer
34					
35	Nippon Kayaku Co., Ltd.	Nogitecan	November 20, 2015	Added indication	Cervical cancer
36					
37	Novartis Pharma K.K.	Panobinostat	July 3, 2015	New approval	Multiple myeloma
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5	Novartis Pharma K.K.	Ruxolitinib	September 24, 2015	Added indication	Polycythemia vera
6					
7	Novartis Pharma K.K.	Dabrafenib	March 28, 2016	New approval	Melanoma
8					
9	Novartis Pharma K.K.	Trametinib	March 28, 2016	New approval	Melanoma
10					
11	Novartis Pharma K.K.	Ceritinib	March 28, 2016	New approval	Non-small cell lung cancer
12					
13	Novartis Pharma K.K.	Everolimus	August 26, 2016	Added indication	Neuro-endocrine tumor
14					
15	Ono Pharmaceutical Co., Ltd.	Nivolumab	February 29, 2016	Added indication	Melanoma
16					
17	Ono Pharmaceutical Co., Ltd.	Nivolumab	December 17, 2015	Added indication	Non-small cell lung cancer
18					
19	Ono Pharmaceutical Co., Ltd.	Carfilzomib	July 4, 2016	New approval	Multiple myeloma
20					
21	Ono Pharmaceutical Co., Ltd.	Nivolumab	August 26, 2016	Added indication	Renal cell cancer
22					
23	Ono Pharmaceutical Co., Ltd.	Nivolumab	December 2, 2016	Added indication	Hodgkin lymphoma
24					
25	Ono Pharmaceutical Co., Ltd.	Nivolumab	March 24, 2017	Added indication	Head and neck cancer
26					
27					
28	Otsuka Pharmaceutical Co., Ltd.	Ponatinib	September 28, 2016	New approval	Chronic myelogenous leukemia
29					
30					Multiple myeloma
31					Non-Hodgkin lymphoma
32	Sanofi K.K.	Plerixafor	December 19, 2016	New approval	Hodgkin
33					lymphoma
34					
35					
36	Sanofi K.K.	Aflibercept Beta	March 30, 2017	New approval	Colorectal cancer
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5	Shionogi & Co., Ltd.	Cyclophosphamide	June 26, 2015	Added indication	Malignant lymphoma
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7	Shionogi & Co., Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
8					
9	Taiho Pharmaceutical Co., Ltd.	Trabectedin	September 28, 2015	New approval	Sarcoma
10					
11	Takeda Pharmaceutical Company Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
12					
13					Prostate cancer
14	Takeda Pharmaceutical Company Ltd.	Leuprorelin	September 28, 2015	New approval	Breast cancer
15					
16	Takeda Pharmaceutical Company Ltd.	Ixazomib	March 30, 2017	New approval	Multiple myeloma
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18	Yakult Honsha Company, Limited.	Oxaliplatin	November 20, 2015	Added indication	Gastric cancer
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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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028805.R2
Article Type:	Research
Date Submitted by the Author:	11-Aug-2019
Complete List of Authors:	Ozaki, Akihiko; Medical Governance Research Institute; Jyoban Hospital of Tokiwa Foundation, Department of Breast Surgery Saito, Hiroaki; Sendai Kousei Hospital, Department of Gastroenterology Onoue, Yosuke; College of Humanities and Sciences, Nihon University Sawano, Toyoaki; Minamisoma Municipal General Hospital, Department of Surgery Shimada, Yuki; Minamisoma Municipal General Hospital, Department of Neurosurgery Somekawa, Yurie; Medical Governance Research Institute Tsuji, Aritsune; Medical Governance Research Institute Tanimoto, Tetsuya; Medical Governance Research Institute
Primary Subject Heading:	Ethics
Secondary Subject Heading:	Oncology, Ethics, Health policy
Keywords:	conflicts of interest, oncology specialist, Japan, industry payment, Japanese Society of Medical Oncology

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Manuscripts

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7 **BMJ Open, Research article**
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9 **Title:**
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12 **Pharmaceutical payments to certified oncology specialists in Japan in 2016: a**
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15 **retrospective observational cross-sectional analysis**
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36 28 Email address: ozakiakihiko@gmail.com.

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40
41
42 30 **Abstract (296 words)**

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45 31 Objective: This study investigated payments made by pharmaceutical companies to

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48 32 oncology specialists in Japan, what the payments were for, and whether the receipt of

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51 33 such payments contravened any Conflict of Interest (COI) regulations.

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6 35 Design, Setting, and Participants: Payment data to physicians, as reported by all
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9 36 pharmaceutical companies belonging to the Japan Pharmaceutical Manufacturers
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12 37 Association (JPMA), were retrospectively extracted for 2016. Of the named individual
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15 38 recipients of payments, all certified oncologists were identified, using certification data
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18 39 from the Japanese Society of Medical Oncology (JSMO). The individual specializations
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21 40 of each of the oncologists was also identified.
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27 42 Outcome: Payments to individual cancer specialists and what they were for were
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30 43 identified. Factors associated with receipt of higher value payments and payment flows
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33 44 to specialties were determined. Companies selling oncology drugs with annual sales of
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36 45 \geq ¥5 billion [£33.9 million, €40.2 million, \$46.0 million] (high revenue generating
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39 46 drugs) were identified.
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45 48 Results: In total, 59 companies made at least one payment to oncologists. Of the 1080
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48 49 oncology specialists identified, 763 (70.6%) received at least one payment, while 317
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51 50 received no payment. Of the 763, some 142 (13.1%) receiving at least ¥1 million
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54 51 [£6,800, €8,000, \$9,200] accounted for 71.5% of the total. After adjustment of
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57 52 covariates, working for university hospitals and cancer hospitals and male gender were
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6 53 key factors associated with larger monetary payments. Payments preferentially targeted
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9 54 on cancer specialties using high revenue generating drugs. The JSMO has its own COI
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12 55 policy for its members but the policy did not mention any specific guidelines for
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15 56 certified oncology specialists.
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21 58 Conclusion: Financial relationships were identified and quantified between
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24 59 pharmaceutical companies and oncology specialists, but the extent and worth varied
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27 60 significantly. Given the frequency and amounts of money involved in such linkages, it
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30 61 would be beneficial for specific COI regulations to be developed and policed for
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33 62 oncologists.
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39 64 **Keywords:** conflict of interest; oncology specialist; Japan; industry payment; Japanese
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42 65 Society of Medical Oncology
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48 67 **Article summary (Strengths and limitations of this study):**
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51 68 ✓ We considered oncology specialists certified by the Japan Society of Medical
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54 69 Oncology, one of the largest professional medical associations in Japan's clinical
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57 70 oncology field.
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7 71 ✓ The authors independently organized payment data for speaking, writing, and
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10 72 consulting work, as published by the major pharmaceutical companies, and created
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12 73 a single uniform payment database.
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15 74 ✓ Accuracy of the affiliations and subspecialties of some oncology specialist in the
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18 75 study year (2016) were estimated using the data on relevant websites and other data
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21 76 sources on the Internet, possibly causing some measurement errors in these
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24 77 variables.
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27 78 ✓ This study only covered limited types of payment data in the single year (2016),
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30 79 which hampered a comprehensive and/or longitudinal analysis of the type and value
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33 80 of the payments among the oncology specialists.

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36 8137
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42 83 **Word count: 4,964**43
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45 8446
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48 85 **Introduction**

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51 86 Increasing global attention is being paid with respect to how pharmaceutical companies
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54 87 (Pharma) operate and their relationships with regard to payments they make to doctors
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57 88 working in national health systems. There is growing concern that specialised
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7 89 physicians receiving financial payments from Pharma commercially connected with
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10 90 their field of expertise may be inadvertently or unethically being influenced and that
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12 91 their impartiality and ability to act in the best interests of their patients is being
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15 92 compromised. The approval earlier this year by the US Federal Drugs Administration
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18 93 (FDA) of anasemnogene abeparvovec-xioi (Zolgensma®), a gene therapy for
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21 94 children less than 2 years old with spinal muscular atrophy which is now the most
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24 95 expensive drug on the market, illustrates the amounts of money that are involved. If a
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27 96 physician prescribes Zolgensma treatment, and a single administration is all that is
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30 97 required, it costs \$2.1 million (£1.6 million, €1.9 million, ¥231.2 million) per patient. In
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33 98 Japan, a new treatment for leukemia and other hematologic cancers was approved in
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36 99 May which will cost ¥33.5 million (£226,800, €269,000, \$307,800). The drug,
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39 100 Tisagenlecleucel (Kymriah®), manufactured and marketed by Novartis Pharma KK, is
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42 101 the most expensive drug on the Japanese market and is covered under Japan's national
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45 102 health insurance. In view of the sums of money involved and the possibility of
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48 103 corruption creeping into the system, there is an increasing need for transparency with
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51 104 respect to all forms of payment, or gifts of any kind, being dispensed by Pharma to
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54 105 physicians. According to the World Medical Association (WMA), "although the
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57 106 cooperation between physicians and commercial enterprises may lead to significant
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6 107 advances in medicine, including the development of new drugs and treatments, it may
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9 108 also result in a conflict of interest (COI) between commercial enterprises and physicians
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12 109 that may have adverse effects on patients' care and the reputation of physicians".
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15 110 Consequently, medical and governmental facilities worldwide are considering steps to
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18 111 help create transparency in the relationship between physicians and the pharmaceutical
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21 112 industry, as exemplified by the USA's Physician Payments Sunshine Act, enacted in
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24 113 2010, and the US government's Open Payments Database
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27 114 (<https://openpaymentsdata.cms.gov>).^{1 2} In Japan, members of the Japan Pharmaceutical
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30 115 Manufacturers Association (JPMA) are attempting to improve the transparency and
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33 116 acceptability of the relationship between corporate activities of Pharma and medical
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36 117 institutions and individual physicians and, in 2015, the JPMA introduced a self-
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39 118 regulatory Guideline for all its members to promote clarity and deeper understanding of
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42 119 the beneficial contribution that Pharma makes to medicine and pharmacy, and so that
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45 120 Pharma activities are conducted with high ethical standards and for maximum benefit to
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48 121 patients.
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54 123 Cancer has been the leading cause of mortality in Japan since 1981. In 2016, there were
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57 124 372,986 cancer deaths in Japan, with malignant neoplasms costing the nation an
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6 125 estimated ¥3.6 trillion [£24.4 billion, €28.9 billion, \$33.1 billion] in medical
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9 126 expenditure. In 2016, lung cancer was the leading cause of cancerous deaths (52,430) in
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11
12 127 males, followed by gastric cancer (29,854) and colorectal cancer (27,026), while
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15 128 colorectal cancer was the leading cause of cancerous death in females (23,073),
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18 129 followed by lung cancer (21,408) and colorectal cancer (17,405).³ The risk factors for
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21 130 cancer are diverse, including tobacco use, infection, obesity, radiation exposure,
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24 131 reproductive and hormonal factors, and other environmental and occupational pollutants
25
26
27 132 and carcinogens.⁴ In Japan, principally because of its ageing population, cancer rates are
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29
30 133 forecast to continue to rise for the foreseeable future.³
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33 134
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36 135 For the pharmaceutical industry, medical and therapeutic practice generates substantial
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39 136 income, allowing it exploit various opportunities to accomplish the goal of the
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42 137 maximization of profits.⁵⁻⁷ From the 1950s, the main business model of the Pharma was
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45 138 the production of low-price drugs to treat diseases and conditions that were primarily
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48 139 chronic and prevalent (e.g. hypertension and diabetes).⁸⁻¹⁰ Following advances in drug
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51 140 development against infectious and chronic diseases, cancer became an ever-increasing
52
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54 141 and major problem, with 17.2 million incidents and 213.2 million cancer-associated
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57 142 disability-adjusted life-years (DALY) lost during 1990-2016 worldwide.¹¹ Pharma
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6 143 therefore adopted a new business model, the discovery and development of anticancer
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9 144 agents that could be sold at extremely high price, but usually for short treatment
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12 145 durations.⁵⁻⁷ This guaranteed a hefty profit in a short timeframe - provided that the drugs
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15 146 would be prescribed and used - while imposing an extraordinarily high cost on patients
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18 147 and health systems.^{5-7 12}
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21 148
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24 149 Physicians remain paramount decision-makers on the demand-side of the
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27 150 pharmaceutical market. It is known that even subtle financial interactions between
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30 151 physicians and a pharmaceutical company can affect their prescribing behavior,¹³⁻¹⁸ and
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33 152 so could encourage irrational or preferential use of a company's drug. Perhaps
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35
36 153 unsurprisingly, given the cost of anticancer drugs, oncologists have latterly become
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39 154 primary targets for approaches from companies with high-cost anticancer products to
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42 155 sell. Indeed, significant financial relationships between such companies and the authors
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45 156 of the oncology Clinical Practice Guidelines (CPGs) have been reported both in the
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48 157 United States and Japan.^{19 20} Given these far from ideal circumstances, there has been a
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51 158 growing need for intervention, in the form of policy implementation and education
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54 159 about the implications of these interactions, to help protect physicians, patients,
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57 160 institutions and the companies themselves.¹⁵⁻¹⁸
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162 Although Japan has the world's third largest pharmaceutical market, with annual sales
163 of \$76 billion in 2017,²¹ its overall scale has been declining at approximately 2%
164 annually.²² To maintain sales in these competitive and tightening markets, forceful
165 advertisement of high-price products, namely novel oncology drugs, has become
166 increasingly important for pharmaceutical companies. Indeed, sales of oncology drugs
167 have recently been rising in Japan, exceeding ¥1 trillion [£6.8 billion, €8.0 billion, \$9.2
168 billion] for the first time in 2016.²³ Furthermore, sales are predicted to increase 1.5–fold
169 in the next decade with the increasing application of immunotherapy in clinical
170 practice.²³ It would therefore be reasonable to assume that pharmaceutical companies
171 will increasingly deploy marketing measures and incentives targeting oncology
172 specialists for the immediate and foreseeable future.

173

174 In Japan, the JPMA encompasses a majority of companies that manufacture brand name
175 drugs. Its members accounted for 80.8% of total pharmaceutical sales in Japan in
176 2015.²⁴ In 2011, the JPMA published a transparency Guideline requiring all member
177 companies to disclose all payments for speaking, writing and consulting made to all
178 individuals, specifying their names and affiliations.²⁵ The Guideline was updated in

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6 179 2015 and made more comprehensive. The aim was to improve the transparency of
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9 180 linkages between pharmaceutical companies and physicians, as in the Open Payments
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12 181 Database in the United States.^{1 2} The 2015 revised JPMA Guideline obliges Pharma to
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15 182 itemize payments made for 1) Research & Development; 2) Academic support; 3)
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18 183 Lecturing/writing/consultancy work; 4) Expenses related to provision of information
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21 184 and 5) Expenses for hospitality, etc. However, the disclosure format, whereby
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24 185 companies involved published the required data on their own individual websites, has
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27 186 differed among and between companies and the aggregated, standardized payment data
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30 187 have not been readily available.²⁶ As a result, an easy examination of
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33 188 company/physicians links and payments in a meaningful way has proved almost
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36 189 impossible.
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42 191 The aims of the current study were: 1) to understand and evaluate the characteristics and
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45 192 distributions of financial payments made by pharmaceutical companies to oncology
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48 193 specialists: 2) to examine whether or not pharmaceutical companies may be making
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51 194 payments to help promote sales of their own products; and 3) to elucidate what Japanese
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54 195 oncology specialists are obliged to disclose with respect to any COI.
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197 **Methods**

198 *Study setting and participants*

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

207

208 *Sources of Payment Data*

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

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6 214 companies included in this study, plus their payment data, are listed in Supplementary
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9 215 Material 1.
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15 217 We obtained each company's data and organized them into a unified, easy-to-compare
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18 218 database. This was done because no data was published as a spreadsheet. Consequently,
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21 219 data with differing character codes were converted into a spreadsheet format and data
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24 220 with no character codes were converted into text files using an Optical Character Reader.
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27 221 Moreover, where data was protected against facsimile or reproduction, we used
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30 222 FullShot10 software (Inbit, CA, USA) to scan photos of the data and converted the data
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33 223 into text files. The accuracy of the re-organized data was confirmed by comparing it
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36 224 with the original data. The database included physicians' names, their main institutional
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39 225 affiliation, payments received, the form of the payments, and the total amount paid. The
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42 226 form of payment was categorized into three types; payment for speaking engagements,
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45 227 payment for writing or publication work, and consulting fees. For the purposes of this
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48 228 study, we converted Japanese yen (¥) to Pounds Sterling (£), Euro (€), and US dollars
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51 229 (\$), using the average monthly exchange rate for 2016, namely ¥147.7 per £1, ¥124.5
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54 230 per €1 and ¥108.8 per US\$1.
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6 232 *Data collection*
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9 233 We examined payment data for all oncology specialists included in this study. We
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12 234 extracted their working institutions and regional locations, along with the year of their
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15 235 certification by the JSMO. We further confirmed the accuracy of such information,
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18 236 collating data from institutional websites and other sources. We determined the sex of
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21 237 all the oncologists, using data from Japan's Ministry of Health, Labour and Welfare,²⁷
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24 238 institutional websites and other sources. We further estimated the primary cancer
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27 239 specialty (respirology, gastroenterology, hematology, breast, etc.) of all oncologists
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30 240 included in the study. We also determined the COI policy of the JSMO prevailing at the
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33 241 time.
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39 243 *Data analysis*
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43 244 To examine the characteristics and distributions of payments, we performed descriptive
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46 245 analyses of the data on an individual oncology specialist and pharmaceutical company
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49 246 basis. We then summarized the characteristics of oncology specialists according to the
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52 247 total monetary value of the payment they received, dividing the patients into the three
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54
55 248 groups; ¥1 million [£6,800, €8,000, \$9,200] or above (High-payment group (HPG)); ¥1
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58 249 – 1 million (Low-payment group (LPG)), and ¥0 (No-payment group (NPG)). In
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6 250 general, ¥1 million is approximately 25% of the median annual income of a Japanese
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9 251 citizen.²⁸
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16 253 Using a multivariate negative binomial regression model, we subsequently examined
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19 254 possible factors associated with the monetary value of the payment to each individual,
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22 255 with sex, institutional place of work, regional working locations, year of experience
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25 256 after board certification, and cancer specialty as covariates. The payment data was
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27
28 257 rounded down as a unit of ¥1 million. Since the payment of those receiving less than ¥1
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31 258 million (Low-payment and No-payment Groups) was regarded as zero in the regression
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34 259 analysis, among this group we further examined possible factors associated with the
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37 260 monetary value of any payment using the same model adopted for the overall
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40 261 population. For this analysis, the payment data was rounded down as a unit of ¥100,000
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43 262 [£677, €803, \$919].
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50 264 For more detailed examination, a Sankey diagram was created to illustrate the
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53 265 distribution of payments to each cancer specialty on an individual company basis. The
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56 266 Sankey diagram is a flow diagram, where band width proportionally represents the flow
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59 267 quantity.²⁹ Payment values from individual companies, according to cancer specialty,
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6 268 are depicted in the bands in the diagram, width being proportional to the total amount of
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9 269 the payment. In addition, to see whether the payment was linked to any specific
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12 270 oncology drugs, we examined such drugs with annual Japanese domestic sales of ¥5
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15 271 billion [£33.9 million, €40.2 million, \$46.0 million] or above (high revenue generating
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18 272 drugs) in fiscal 2016, and if each drug was covered under the Japanese National Health
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21 273 Insurance scheme in specific oncology subspecialty by the end of the same fiscal year
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24 274 (March 31, 2017). We further examined newly-approved drugs and drugs with a new
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27 275 indication added during the fiscal years of 2015 and 2016 (April 1, 2015 to March 31,
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30 276 2017).

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35 36 37 278 *Human subject involvement*

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40 279 The present study is a retrospective analysis of existing databases and public domain
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43 280 information. No patients or any other individuals other than oncology specialists
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46 281 identified in the public domain, and whose names are not identified in this report, were
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49 282 included in the study.

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53 54 55 284 **Results**

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6 285 The JSMO had over 9,000 members at the time the study was undertaken, with 1081
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9 286 physicians having been Board Certified as oncology specialists. We excluded one
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12 287 oncologist whose professional affiliation we were unable to confirm, and he did not
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15 288 receive any payment from the pharmaceutical companies. Thus, we included a total of
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18 289 1,080 specialist oncologists in our analyses.
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24 291 Table 1 summarizes the details of certified oncologists and payments from Japanese
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27 292 pharmaceutical firms. Of the 1,080 individuals involved, 907 were men (84.0%) and
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30 293 173 (16.0%) were women. Of the total, 442 (40.9%), 183 (16.9%), and 455 (42.1%)
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33 294 worked for university hospitals, cancer hospitals, and other institutions, respectively. In
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36 295 2016, the most common specialty was respiratory (285, 26.4%), followed by
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39 296 gastroenterology (278, 25.7%) and hematology (250, 23.2%).
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45 298 A total of 7,325 payments were recorded, the total monetary value being ¥585,453,314
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48 299 [£3,963,800, €4,702,436, \$5,381,005]. Of this total, ¥467,802,690 [£3,167,249,
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51 300 €3,757,451, \$4,299,657] was for speaking engagements, ¥94,682,807 [£641,048,
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54 301 €760,504, \$870,246] was for consulting services, and ¥22,266,186 [£150,753, €178,845,
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57 302 \$204,652] was paid for writing work. The median monetary value and count of an
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6 303 individual payment was ¥120,016 [£813, €964, \$1,103]. (interquartile range (IQR) ¥ 0 –
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9 304 ¥449,378 [£3,043, €3,609, \$4,130] and 2 (IQR 0–7), respectively.
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15 306 Of the 1,080 individuals, 763 (70.6%) received at least one payment. Furthermore, 142
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18 307 (13.1%) received payments totaling \geq ¥1 million, while 19 (1.8%) received \geq ¥5 million
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21 308 [£33,900, €40,200, \$46,000]. Two individuals (0.2%) received \geq ¥10 million [£67,700,
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24 309 €80,300, \$91,900].
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30 311 Respiriology was the specialty which attracted the largest payment (¥216,806,522
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33 312 [£1,467,884, €1,741,418, \$1,992,707] from the pharmaceutical companies, followed by
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36 313 gastroenterology (¥139,690,202 [£945,770, €1,122,010, \$1,283,917.00] and
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39 314 hematology (¥119,219,713 [£807,175, €957,588, \$1,095,769]).
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45 316 Table 2 summarizes the monetary values and counts of payments made by the 78
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48 317 pharmaceutical companies. In total, 59 (75.6%) companies made at least one payment to
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51 318 oncology specialists. The Chugai Pharmaceutical Co. Ltd., a subsidiary of F. Hoffmann-
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54 319 La Roche Ltd, made the largest accumulated payment of ¥103,830,493 [£702,982, €
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57 320 833,980, \$954,324]. The median monetary value and count among the 78 companies
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6 321 was ¥645,946 [£4,373, €5,188, \$5,937] (IQR ¥33,410 [£226, €268, \$307] – ¥5,196,201
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9 322 [£35,181, €41,737, \$47,759] and 10 (IQR 1 – 71), respectively.
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15 324 Table 3 ranks the oncology specialists according to the monetary value of the payments
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18 325 they received. In the HPG (N=142), females accounted for only 6.3% (9) of the total,
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21 326 while in the LPG (N=621), females accounted for 10.6% (66) of the total. However,
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24 327 females accounted for 30.9% (99) in the NPG (N=317). With respect to male recipients,
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27 328 75.9% (688/907) received at least one payment, compared to only 43.4% of females
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30 329 (75/173). Of the oncologists in the HPG, 52.8% (75) worked for university hospitals
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33 330 and 28.2% (40) worked for cancer hospitals: these figures were higher than those seen
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36 331 in the other two groups. Further, while only 19.7% (28) of the specialists in the HPG
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39 332 were certified during the previous five years (2012 to 2016), 49.4% (307) and 60.3%
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42 333 (191) of individuals in the LPG and NPG respectively were certified during these five
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45 334 years. The proportion of specialist respiratory oncologists was larger in the HPG (55,
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48 335 38.7%) than in either the LPG (165, 26.6%) or NPG (65, 20.5%).
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6 337 In the HPG, the total monetary value paid and number of payments were ¥418,345,258
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9 338 [£2,832,398, €3,360,203, \$3,845,085] and 4,466, respectively, accounting for 71.5%
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12 339 and 61.0% of the totals.
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18 341 Table 4 displays findings of the multivariate regression analyses for the monetary value
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21 342 of payments. Female oncologists tended to receive a smaller value of payments than
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24 343 their male counterparts (relative monetary value [RMV] 0.40, 95% CI 0.20 – 0.79).
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27 344 Oncologists working for university hospitals (RMV 5.78, 95% CI 3.34 – 10.02) and
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30 345 those working for cancer hospitals (RMV 5.47, 95% CI 3.30 – 9.06) also tended to
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33 346 receive higher payments. Oncologists with longer experience after board certification
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36 347 were significantly more likely to receive larger payments compared with those with
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39 348 shorter experience (RMV 1.40, 95% CI 1.30 – 1.50). Those working in hematology
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42 349 were likely to receive smaller payments than those working in respirology (RMV 0.49,
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45 350 95% CI 0.30 – 0.83). In the LPG and NPG, there were no significant differences in the
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48 351 monetary value of the payments with respect to the type of affiliation of recipients.
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54 353 Figure 1 displays payment distributions to each cancer specialty on an individual
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57 354 company basis. Details of the payments are provided in Supplementary Material 2.
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7 355 Further, in Supplementary Material 3, we summarize the list of high revenue generating
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9 356 oncology drugs. Chugai Pharmaceutical Co., Ltd. made the largest specialty payment of
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12 357 ¥ 103,830,493 [£702,982, €833,980, \$954,324] and the top four specialties were
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15 358 gastroenterology (¥34,760,717 [£235,347, €279,203, \$319,492], 33.5%), respirology
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18 359 (¥32,937,605 [£223,003, €264,559, \$302,735], 31.7%), hematology (¥17,702,450
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21 360 [£119,854, € 142,188, \$162,706], 17.0%), and breast cancer (¥10,548,519 [£71,419, €
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24 361 84,727, \$96,953], 12.0%). The Chugai company manufactured eight high revenue
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27 362 generating oncology drugs (Supplementary Material 3), and four, three, one, and five
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30 363 drugs were respectively covered under the National Health Insurance scheme for the
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33 364 field of gastroenterology, respirology, hematology and breast cancer. Nivolumab
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36 365 (Opdivo®), manufactured by the Ono Pharmaceutical Co., Ltd., mainly used in lung
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39 366 cancer and melanoma, had the largest domestic sales in 2016 (¥103.9 billion [£703.5
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42 367 million, €834.5 million, \$955.0 million]). The total monetary value of the company's
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45 368 payments was ¥47,831,737 [£323,844, €384,191, \$439,630], (representing fourth place
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48 369 in the payment table), of which ¥29,657,836 [£200,798, €238,216, \$272,590] (62.0%)
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51 370 was specifically distributed to respirology specialists. All of the top eight companies
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54 371 with regard to the monetary value of the payments (Supplementary Material 2) had at
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57 372 least one drug which was newly approved or that had an added anticancer indication
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6 373 under the National Health Insurance scheme in the fiscal years of 2015 and 2016
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9 374 (Supplementary Material 4). While AstraZeneca Plc. had no high revenue generating
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12 375 oncology drugs (Supplementary Material 3), vandetanib (Caprelsa®) and osimertinib
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15 376 (Tagrisso®) were newly approved for thyroid cancer in September, 2015 and non-small
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18 377 cell lung cancer in March, 2016, respectively (Supplementary Material 4). The total
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21 378 monetary value of the company's payments was second, accounting for ¥51,928,785
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24 379 [£351,583, €417,099, \$477,287]. Of the total, 84.8% (¥44,013,864 [£297,995, €353,525,
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27 380 \$404,539]) was specifically allocated to oncologists with a specialism in respirology.
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33 382 The JSMO has established a guideline on COI disclosure for its members which
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36 383 requires them to disclose any COI associated with publications and other research
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39 384 presentations. Further, Executive Board members, auditors, and other high-level
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42 385 members, as well as Presidents and Vice-Presidents of conferences and committee
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45 386 members operating under the JSMO are required to disclose any COI associated with
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48 387 their work and positions. These include, with respect to any for-profit organization,
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51 388 reporting any 1) position as an officer or advisor, 2) stock ownership, 3) patent royalties
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54 389 or licensing fees, 4) honoraria (e.g. lecture fees), 5) fees paid for any writing or
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57 390 publication work, 6) receipt of research funding, 7) advisory fees or financial
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6 391 remuneration in exchange for testimony, 8) acceptance of researchers from any for-
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9 392 profit enterprise, 9) endowed chairs offered, and 10) any remuneration (travel, gifts, or
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12 393 other in-kind payments not directly related to research). However, there are no rules
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15 394 specifically referring to oncology specialists.
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396 **Discussion**

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

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402 The proportion of oncologists receiving payments was larger compared with general
403 physicians in the US (48.0%)³⁰ and Japan (33.3%).³¹ However, the proportion was
404 slightly smaller than that of NCCN oncology CPG authors in the US (86.4%).¹⁹

405 Although the mean value of payments in our study was approximately half of that of the
406 CPG authors (\$4,982 [data not shown] vs.\$10,011), a simple comparison is not valid, as
407 our analysis only covered data for speaking, writing and consultancy work. It did not
408 include payments related to meals, transportation and accommodation, stock ownership,

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6 409 investment interest, or payments from medical device companies, as is compiled in the
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9 410 US's Open Payments database.³⁰ The CPG authors strongly influence oncology practice,
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12 411 both in the US and internationally,³² by recommending treatment algorithms. They may
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15 412 well be identified as prime targets for representatives of Pharma attempting to promote
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18 413 the sale of their anticancer products. It is thus reasonable to assume that Japanese
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21 414 Pharma with similar anticancer interests may well be trying to target oncology
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24 415 specialists in an attempt to help boost the sales and use of their specific products.
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30 417 We observed a large disparity in payments to specialists. Those receiving ¥1 million or
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33 418 more accounted for 13.1% of all oncologists studied but received 71.5% of the total
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36 419 paid. Oncologists working for university hospitals and those working for cancer
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39 420 hospitals similarly received large value payments. In Japan, cancer centers are generally
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42 421 more likely to treat more cancer patients compared to university hospitals. Indeed,
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45 422 cancer centers top the nationwide ratings for treatments of most of the common cancers,
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48 423 including lung, colon, gastric, and breast cancer.³³ In contrast, university hospitals are
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51 424 regarded as symbols of academic excellence and authority, and medical school
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54 425 professors traditionally have a strong influence on both physicians and medical practice
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57 426 in their field of expertise. They are more influential in setting treatment protocols which
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6 427 are usually followed without question by less senior medical staff nationwide. Thus, our
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9 428 findings suggest that Japanese pharmaceutical companies have placed emphasis on
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12 429 expertise and authority, as well as clinical experience, in the selection of targets for their
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15 430 promotional activities.
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21 432 A particularly significant finding was that a smaller proportion of female oncologists
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24 433 received payments from Pharma compared to their male colleagues. Furthermore,
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27 434 women also tended to receive smaller payment amounts than men. These findings are in
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30 435 line with similar studies performed in the US.^{34 35} In the relatively unique, patriarchal
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33 436 Japanese society, there may be very specific reasons for these results. Firstly, there are
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36 437 far fewer female oncologists than males and they have considerably less spare time for
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39 438 industry-related work due to women needing to fulfill their socially-perceived duty to
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42 439 be the main person responsible for raising any children in the family.³⁶ Further, Pharma
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45 440 may tend to target men rather than women³⁴ because in Japan's male-dominated society,
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48 441 the status of women has traditionally been low, and their contribution, presence and
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51 442 influence in biomedicine and the higher echelons of power and influence has not been
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54 443 actively encouraged.^{37 38}
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6 445 We found that respirology attracted the greatest financial outlay. In Japan, lung cancer
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9 446 is of primary concern at present, covering a large patient volume and consequently
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12 447 attracting multiple novel oncology drugs, such as alectinib (Alecensa®) (Chugai
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15 448 Pharmaceutical Co., Ltd., [approved 2014]), nivolumab (Opdivo®) (Ono
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18 449 Pharmaceutical Co., Ltd, [approved 2015]), afatinib (Gilotrif®) (Nippon Boehringer
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21 450 Ingelheim Co., Ltd., [approved 2016]), ceritinib (Zykadia®) (Novartis Pharma K.K.,
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24 451 [approved 2016]), osimertinib (Tagrisso®) (AstraZeneca plc, [approved 2016]),
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27 452 pembrolizumab (Keytruda®) (MSD K.K., [approved 2016]), ramucirumab
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30 453 (Cyramza®) (Eli Lilly Japan K.K., [approved 2016]), all for non-small cell lung cancer
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33 454 (Supplementary Materials 3 & 4). As such, for the pharmaceutical companies, this field
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36 455 is a critical yet highly competitive target in any strategy to maximize the cost-
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39 456 effectiveness of their promotional endeavors.
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45 458 The examples of Chugai Pharmaceutical and Ono Pharmaceutical chiefly support the
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48 459 belief that there is an association between the value and destination of payments
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51 460 dependent on the products the companies in question manufacture. In contrast, the
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54 461 example of AstraZeneca adds credence to the notion that that funds were mainly
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57 462 allocated to promote their novel product: osimertinib (Tagrisso®) was approved for
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6 463 non-small cell lung cancer in March 2016. Indeed, 84.8% of the company's total
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9 464 payment was allocated to respiratory specialists.
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15 466 As we have demonstrated, there are extensive financial relationships between
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18 467 pharmaceutical companies and oncologists in Japan. It is true that the receipt of
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21 468 payments by physicians in Japan is not illegal, especially as they are supposedly given
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24 469 as remuneration for work undertaken or services rendered. However, we believe that
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27 470 there is an ethical problem inherent in such relationships, given that this practice can be
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30 471 seen by the public and neutral observers as being instigated and developed to possibly
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33 472 end up expanding the profit of pharmaceutical companies, rather than promoting the
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36 473 health and well-being of patients. Indeed, even a subtle but reputable financial
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39 474 relationship with the industry, such as collaborating in a field trial, could bias a
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42 475 physician's prescription patterns in a manner that benefits the companies.¹³⁻¹⁸
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45 476 Oncologists handle extraordinary and very potent life-saving drugs, and have a degree
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48 477 of autonomy in their prescribing actions. Their decisions substantially influence the
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51 478 treatment and outcome for their patients, as well as having significant economic impact
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54 479 due to the high cost of anticancer medications.⁵⁻⁷ It would therefore appear sensible to
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57 480 have regulations in place which necessitate the open and accessible reporting of any
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6 481 financial dealings between physicians and Pharma, so as to avoid any potential
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9 482 nefarious or underhand behavior or undue pressure on physicians to alter their usual
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12 483 treatment practices. Indeed, it is possible that these arrangements may have contributed
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15 484 to the multiple cases of scientific misconduct that have recently been reported in Japan.
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18 485 The most infamous case was when employee misconduct was discovered in a series of
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21 486 clinical trials for Valsartan, an antihypertensive medication manufactured by Novartis
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24 487 Pharma KK, leading to a retraction of the associated academic papers.^{39 40} Also, the
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27 488 company illegally (or unethically) obtained the information about patients participating
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30 489 in another clinical trial for chronic myelogenous leukemia using nilotinib (Tasigna®)
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33 490 from a university hospital in Japan.^{41 42} A breast cancer clinical trial (CREATE-X trial)
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36 491 with a questionable pharmaceutical payment has also been identified.^{43 44}
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42 493 Since January, the new regulations in Japan have already been weakened by allowing
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45 494 Pharma to aggregate payment data they should publish into a single amount, making
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48 495 matters much less transparent.⁴⁵ To prevent similar cases in future, we call for the
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51 496 implementation of a transparent, independent mechanism that would enable a
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54 497 comprehensive assessment of any and all payments being made by any pharmaceutical
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57 498 company to any individual physician or, for that matter, medical institution where the
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6 499 company's products may be used - and not just with respect to oncology. Ideally, these
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9 500 actions should be mandatory and legally-binding on the side of both the company and
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12 501 physician. New schemes along these lines, such as the US's Open Payments Database,
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15 502 may prove successful but it is too soon to know.⁴⁶ The Disclosure UK mechanism may
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18 503 not prove to be so effective as it is voluntary.⁴⁷ Additionally, given that such
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21 504 mechanisms allow for direct comparison between what is allegedly paid and what is
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24 505 allegedly received, any new system will probably necessitate a fair, equitable and timely
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27 506 mechanism for dispute settlement, probably involving the use of third parties.⁴⁴
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31 508 **Study Limitations**

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36 509 Several limitations in this preliminary study should be acknowledged. First, there could
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39 510 be measurement errors in the affiliations and subspecialties of the included specialists,
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42 511 as we collated these data in the study year (2016), using the websites and other data
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45 512 sources on the Internet. Second, there might be minor measurement errors in the
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48 513 payment database as well. Most of the pharmaceutical companies involved did not
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51 514 disclose their payment data in a uniform or readily available format. As a result, we
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54 515 manually entered all the payment data from a variety of formats, and, despite repeated
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57 516 and careful review, the database may include minor errors. Third, the present research
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6 517 analyzed only limited payment types, namely speaking, writing and consultancy work.
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9 518 Currently, Japanese pharmaceutical companies do not disclose any payment data for
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12 519 stock holdings, royalties, individual data for costs of meals, transportation and
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15 520 accommodation, etc. As, unlike the pharmaceutical companies, the JMSO and other
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18 521 similar academic and learned societies in Japan, where such data may be registered,
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21 522 refuse to open their databases on payments to public scrutiny, we were not able to
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24 523 consider these data in this study. Fourth, most of the pharmaceutical companies only
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27 524 publish single year data so we could only consider payments made in fiscal 2016. To
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30 525 understand temporal trends and the extent and distribution of pharmaceutical company
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33 526 payments, a continuous assessment of the payment data is warranted in future.
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39 528 **Concluding remarks**

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42 529 Japanese certified oncologists receive financial payments directly from pharmaceutical
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45 530 companies, usually from companies active in the specialist field of the physician in
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48 531 question. In today's prevailing climate of Fake News, inaccurate scientific data,
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51 532 Vaccine Hesitancy, and suspicion about many financial dealings involving Pharma, this
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54 533 raises several queries with regard to ethical, medical, and legal issues. The value and
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57 534 specialty targets of the payments varied substantially, which also raises yet more
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6 535 questions as to why. We believe that the lessons learned from our analyses should be
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9 536 shared among the global medical community to help put in place safeguards to prevent
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12 537 any form of inducements from the pharmaceutical industry and to help protect
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15 538 physicians from outside influences. It is essential to establish a robust, comprehensive
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18 539 and legally-binding system for identifying and avoiding any and all potential COIs, of
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21 540 any nature, involving physicians or other medical professionals, both in Japan and
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24 541 internationally. While it is too early to evaluate whether similar systems, such as the
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27 542 US-based Open Payments Database, will be truly effective, financial transparency is a
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30 543 fundamental component in illustrating that there is an open, honest and ethically correct
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33 544 relationship between pharmaceutical companies and physicians. A more comprehensive
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36 545 study is planned, to include all Japanese oncologists, to try and confirm our findings and
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39 546 to help identify the best way forward to ensure that COIs are minimized and so that
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42 547 physicians and pharmaceutical companies can work harmoniously and synergistically to
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45 548 provide Japan with the best cancer prophylaxis, treatment and cures possible.
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51 **Ethics approval**

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54 551 This study was approved by the Institutional Review Board of the Medical Governance
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57 552 Research Institute (MEGRI) on 16th May 2018.
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554 **Author contributors**

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

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

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

560 A.O. drafted the manuscript.

561

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585 **Data availability statement**

586 The datasets analyzed during the current study are available from the corresponding
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For peer review only

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6 **590 Figure legends**
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9 **591 Figure 1.** Distribution of payments to each subspecialty on an individual company basis.
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12 **592** The companies and specialties are sorted in descending order with regard to payment
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15 **593** value (proportionally expressed in the box height and band width in Figure 1). Band
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18 **594** color represents the payment destination specialties. Due to space limitations, names of
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21 **595** companies with payment values of less than ¥10 million (£67,700, €80,300, \$91,900)
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24 **596** 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 (¥ [£],	120,016 [813] (0 [0] – 449,378
Interquartile range)	[3,043])
Median count per individual specialist (Interquartile	2 (0–7)
range)	
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

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

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

748

749 **Table 2. Companies making a payment to oncology specialists and monetary value**
 750 **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

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6	Novo Nordisk Pharma Ltd.	474,360 [3,212]	8
7	Sanwa Kagaku Kenkyusho Co., Ltd.	445,480 [3,016]	4
8	Aska Pharmaceutical Co., Ltd.	423,206 [2,865]	6
9	Shire Japan K.K.	367,521 [2,488]	5
10	Nihon Pharmaceutical Co., Ltd.	311,836 [2,111]	8
11	Nippon Chemiphar Co., Ltd.	278,425 [1,885]	3
12	Ayumi Pharmaceutical Corporation	226,864 [1,536]	3
13	Mylan Seiyaku Ltd.	206,240 [1,396]	4
14	Kracie Holdings, Ltd.	134,056 [908]	2
15	GlaxoSmithKline K.K.	111,370 [754]	2
16	Minophagen Pharmaceutical Co.	110,440 [748]	2
17	Maruho Co., Ltd.	103,120 [698]	1
18	Torii Pharmaceutical Co., Ltd.	102,260 [692]	2
19	EN Otsuka Pharmaceutical Co., Ltd.	89,096 [603]	2
20	Kaken Pharmaceutical Co., Ltd.	77,959 [528]	1
21	Toray Industries, Inc.	77,080 [522]	1
22	Santen Pharmaceutical Co., Ltd.	51,560 [349]	1
23	Toyama Chemical Co., Ltd.	33,410 [226]	1
24	Bee Brand Medico Dental. Co., Ltd.	0 [0]	0
25	Biofermin Seiyaku Co., Ltd.	0 [0]	0
26	Fujimoto Pharmaceutical Corporation	0 [0]	0
27	Fuso Pharmaceutical Industries, Ltd.	0 [0]	0
28	Japan Tobacco Inc.	0 [0]	0
29	Kyoto Pharmaceutical Industries, Ltd.	0 [0]	0
30	Maruishi Pharmaceutical Co., Ltd.	0 [0]	0
31	Nippon Zoki Pharmaceutical Co., Ltd.	0 [0]	0
32	Otsuka Pharmaceutical Co., Ltd.	0 [0]	0
33	Otsuka Pharmaceutical Factory, Inc.	0 [0]	0
34	POLA-Pharma.	0 [0]	0
35	Research Institute for Microbial Diseases	0 [0]	0
36	Seikagaku Corporation	0 [0]	0
37	Senju Pharmaceutical Co., Ltd.	0 [0]	0
38	Taisho Pharmaceutical Co., Ltd.	0 [0]	0
39	Teikoku Seiyaku Co., Ltd.	0 [0]	0
40	Toa Eiyo Ltd.	0 [0]	0
41	UCB Japan Co., Ltd.	0 [0]	0
42	Wakamoto Pharmaceutical Co., Ltd.	0 [0]	0
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49	751	We converted Japanese yen (¥) to Pound Sterling (£), using the average monthly	
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52	752	exchange rate for 2016, namely ¥147.7 yen per £1.	
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754 **Table 3. Characteristics of oncology specialists and pharmaceutical company payments received in 2016, according to the**

755 **monetary value of the payment**

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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)

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4	Kyushu	16 (11.3)	80 (12.9)	39 (12.3)
5	Year of certification (N, %)			
6				
7	2006	22 (15.5)	21 (3.4)	2 (0.6)
8	2007	15 (10.6)	46 (7.4)	16 (5.1)
9	2008	19 (13.4)	38 (6.1)	14 (4.4)
10	2009	19 (13.4)	56 (9.0)	23 (7.3)
11	2010	23 (16.2)	80 (12.9)	30 (9.5)
12	2011	16 (11.3)	73 (11.8)	41 (12.9)
13	2012	9 (6.3)	72 (11.6)	43 (13.6)
14	2013	9 (6.3)	79 (12.7)	55 (17.4)
15	2014	5 (3.5)	65 (10.5)	28 (8.8)
16	2015	2 (1.4)	51 (8.2)	32 (10.1)
17	2016	3 (2.1)	40 (6.4)	33 (10.4)
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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 pharmaceuticalpayment

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
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4	Interquartile range)	[24,927])	[2,579])
5	Median count (Interquartile range)	24 (19 – 38)	3 (2 – 6)
6	Monetary value of payment according to		
7	specialties (¥ [£], %)		
8			
9			
10	Respirology	169,761,707 [1,149,368], 40.6	47,044,815 [318,516], 28.2
11			
12	Gastroenterology	92,334,612 [625,150], 22.1	47,335,590 [320,485], 28.3
13			
14	Hematology	81,963,421 [554,932], 19.6	37,256,292 [252,243], 22.3
15			
16	Breast	42,090,455 [284,973], 10.1	7,197,206 [48,729], 4.3
17			
18	Head and neck	8,689,962 [58,835], 2.1	523,439 [3,544], 0.3
19			
20	Gynaecology	0 [0], 0	570,533 [3,863], 0.3
21			
22	Urology	5,527,458 [37,424], 1.3	2,334,827 [15,808], 1.4
23			
24	Dermatology	0 [0], 0	562,502 [3,808], 0.3
25			
26	Other or undetermined	17,977,643 [121,717], 4.3	24,262,852 [164,271], 14.5
27			

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

758 **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)*

759 † Other or undetermined specialties included Head and neck cancer, Gynaecology, Urology and Dermatology. Due to the small number

760 of physicians in these four specialties, they were included in the “other or undetermined” category; CI=Confidence interval; * <0.05, **

761 <0.01, *** <0.001

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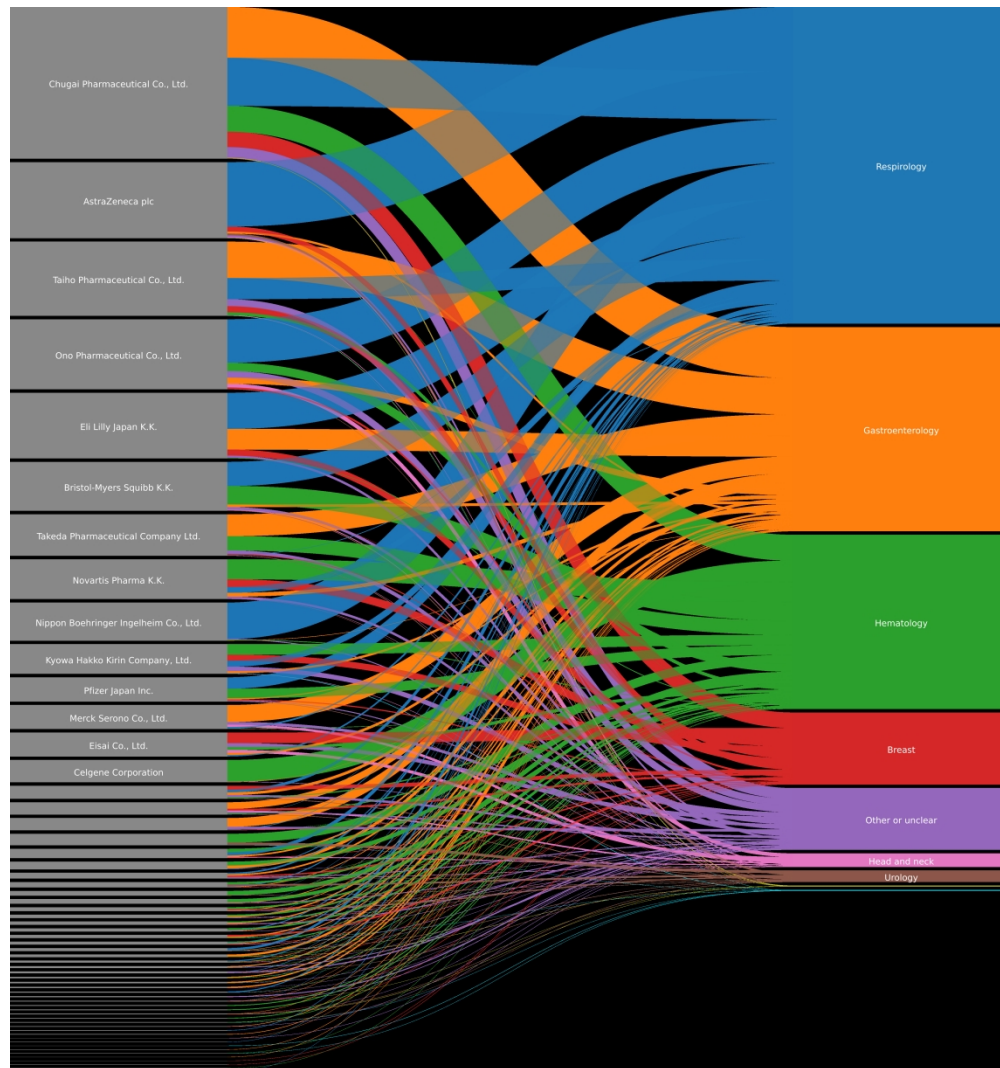


Figure 1. Distribution of payments to each subspecialty on an individual company basis. The companies and specialties are sorted in descending order with regard to payment value (proportionally expressed in the box height and band width in Figure 1). Band color represents the payment destination specialties.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

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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]

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4											
5	Kyowa Hakko Kirin Company, Ltd.	4,065,005	1,425,536 [9,652]	7,127,681	4,181,946	111,370	0 [0]	0 [0]	222,740	3,073,817	20,208,095
6		[27,522]		[48,258]	[28,314]	[754]			[1,508]	[20,811]	[136,819]
7											
8	Pfizer Japan Inc.	7,782,876	788,768 [5,340]	6,543,478	638,311	0 [0]	0 [0]	217,649	0 [0]	538,396	16,509,478
9		[52,694]		[44,302]	[4,322]			[1,474]		[3,645]	[111,777]
10											
11	Merck Serono Co., Ltd.	1,002,330	11,588,836	245,014	111,370	1,603,728	0 [0]	0 [0]	0 [0]	1,826,468	16,377,746
12		[6,786]	[78,462]	[1,659]	[754]	[10,858]				[12,366]	[110,885]
13											
14	Eisai Co., Ltd.	890,961	1,624,796	1,982,386	7,244,821	1,948,977	0 [0]	0 [0]	0 [0]	2,617,195	16,309,136
15		[6,032]	[11,001]	[13,422]	[49,051]	[13,196]				[17,720]	[110,421]
16											
17	Celgene Corporation	0 [0]	226,864 [1,536]	14,722,632	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	257,800	15,207,296
18				[99,679]						[1,745]	[102,961]
19											
20	Daiichi Sankyo Company, Limited.	1,826,473	1,789,335	700,236	2,615,204	0 [0]	0 [0]	389,796	0 [0]	1,451,057	8,772,101
21		[12,366]	[12,115]	[4,741]	[17,706]			[2,639]		[9,824]	[59,391]
22											
23	Bayer Yakuhin, Ltd.	77,959 [528]	4,397,978	645,946	1,264,054	863,118	0 [0]	278,425	0 [0]	813,001	8,340,481
24			[29,776]	[4,373]	[8,558]	[5,844]		[1,885]		[5,504]	[56,469]
25											
26	Yakult Honsha Company, Limited.	412,486	5,946,230	51,561 [349]	381,548	0 [0]	0 [0]	0 [0]	0 [0]	1,526,201	8,318,026
27		[2,793]	[40,259]		[2,583]					[10,333]	[56,317]
28											
29	Janssen Pharmaceutical K.K.	0 [0]	0 [0]	5,924,886	0 [0]	0 [0]	0 [0]	1,742,945	55,685 [377]	0 [0]	7,723,516
30				[40,114]				[11,801]			[52,292]
31											
32	MSD K.K.	2,224,616	946,647 [6,409]	2,338,771	278,425	529,009	0 [0]	0 [0]	0 [0]	0 [0]	6,317,468
33		[15,062]		[15,835]	[1,885]	[3,582]					[42,772]
34											
35	Sumitomo Dainippon Pharma Co., Ltd.	478,658	1,926,703	2,712,881	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959	5,196,201
36		[3,241]	[13,045]	[18,368]						[528]	[35,181]
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5	Nippon Kayaku Co., Ltd.	974,487	958,195 [6,487]	55,685 [377]	855,809	222,740	0 [0]	222,740	0 [0]	579,124	3,868,780
6		[6,598]			[5,794]	[1,508]		[1,508]		[3,921]	[26,194]
7											
8	Astellas Pharma Inc.	600,000	340,000 [2,302]	1,400,000	100,000	0 [0]	0 [0]	1,100,000	0 [0]	50,000	3,590,000
9		[4,062]		[9,479]	[677]			[7,448]		[339]	[24,306]
10											
11	Nippon Shinyaku Co., Ltd.	33,411 [226]	33,411 [226]	2,851,072	0 [0]	0 [0]	0 [0]	211,603	0 [0]	0 [0]	3,129,497
12				[19,303]				[1,433]			[21,188]
13											
14	Asahi Kasei Pharma Corporation	77,959 [528]	326,155 [2,208]	2,138,304	0 [0]	0 [0]	0 [0]	111,370	0 [0]	448,664	3,102,452
15				[14,477]				[754]		[3,038]	[21,005]
16											
17	Sanofi K.K.	0 [0]	312,500 [2,116]	960,000	370,000	100,000	0 [0]	750,000	0 [0]	100,000	2,592,500
18				[6,500]	[2,505]	[677]		[5,078]		[677]	[17,552]
19											
20	Otsuka Holdings Co., Ltd. ^e	100,000 [677]	770,000 [5,213]	1,087,912	0 [0]	46,286	0 [0]	0 [0]	0 [0]	200,000	2,204,198
21				[7,366]		[313]				[1,354]	[14,923]
22											
23	Mochida Pharmaceutical Co., Ltd.	0 [0]	679,357 [4,600]	790,727	111,370	0 [0]	0 [0]	0 [0]	0 [0]	567,987	2,149,441
24				[5,354]	[754]					[3,846]	[14,553]
25											
26	Peijin Pharma Limited.	550,000	359,790 [2,436]	1,020,000	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	170,000	2,099,790
27		[3,724]		[6,906]						[1,151]	[14,217]
28											
29	AbbVie GK,	0 [0]	735,042 [4,977]	245,014	1,046,885	0 [0]	0 [0]	0 [0]	55,685 [377]	0 [0]	2,082,626
30				[1,659]	[7,088]						[14,100]
31											
32	Shionogi & Co., Ltd.	556,848	443,416 [3,002]	567,160	206,240	0 [0]	0 [0]	0 [0]	0 [0]	175,304	1,948,968
33		[3,770]		[3,840]	[1,396]					[1,187]	[13,195]
34											
35	Kyorin Pharmaceutical Co., Ltd.	1,443,680	144,368 [977]	72,184 [489]	0 [0]	0 [0]	0 [0]	206,241	0 [0]	51,560	1,918,033
36		[9,774]						[1,396]		[349]	[12,986]
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5	Tsumura & Co.	33,411 [226]	1,347,578 [9,124]	167,055	55,685	0 [0]	77,959 [528]	0 [0]	0 [0]	0 [0]	1,681,688
6				[1,131]	[377]						[11,386]
7											
8	Meiji Seika Pharma Co., Ltd.	649,656	154,680 [1,047]	278,424	103,120	0 [0]	0 [0]	0 [0]	0 [0]	103,120	1,289,000
9		[4,398]		[1,885]	[698]					[698]	[8,727]
10											
11	Terumo Corporation	110,440 [748]	585,332 [3,963]	77,308 [523]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	441,760	1,214,840
12										[2,991]	[8,225]
13											
14	Kissei Pharmaceutical Co., Ltd.	222,740	55,685 [377]	0 [0]	0 [0]	0 [0]	0 [0]	144,781	0 [0]	701,634	1,124,840
15		[1,508]						[980]		[4,750]	[7,616]
16											
17	Zeria Pharmaceutical Co., Ltd.	77,959 [528]	645,946 [4,373]	222,740	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	946,645
18				[1,508]							[6,409]
19											
20	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	935,508
21										[754]	[6,334]
22											
23	EA Pharma Co., Ltd.	0 [0]	752,776 [5,097]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	30,936	783,712
24										[209]	[5,306]
25											
26	Taisho Toyama Pharmaceutical Co., Ltd.	590,261	0 [0]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,959	701,631
27		[3,996]								[528]	[4,750]
28											
29	Kowa Company, Ltd.	0 [0]	33,411 [226]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	556,851	590,262
30										[3,770]	[3,996]
31											
32	Hisamitsu Pharmaceutical Co., Inc.	22,274 [151]	89,096 [603]	0 [0]	167,055	0 [0]	15,591 [106]	0 [0]	0 [0]	245,014	539,030
33					[1131]					[1,659]	[3,649]
34											
35	Novo Nordisk Pharma Ltd.	0 [0]	0 [0]	474,360	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	474,360
36				[3,212]							[3,212]
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5	Sanwa Kagaku Kenkyusho Co., Ltd.	0 [0]	0 [0]	445,480	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	445,480
6			[3,016]							[3,016]
7										
8	Aska Pharmaceutical Co., Ltd.	0 [0]	111,370 [754]	0 [0]	77,959	0 [0]	33,411 [226]	144,781	0 [0]	55,685
9					[528]			[980]		[377]
10										
11	Shire Japan K.K.	0 [0]	0 [0]	367,521	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	367,521
12				[2,488]						[2,488]
13										
14	Nihon Pharmaceutical Co., Ltd.	0 [0]	0 [0]	245,014	0 [0]	0 [0]	0 [0]	33,411	33,411 [226]	0 [0]
15				[1,659]				[226]		[2,111]
16										
17	Nippon Chemiphar Co., Ltd.	0 [0]	167,055 [1,131]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370
18										[754]
19										
20	Ayumi Pharmaceutical Corporation	226,864	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	226,864
21		[1,536]								[1,536]
22										
23	Mylan Seiyaku Ltd.	0 [0]	206,240 [1,396]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	206,240
24										[1,396]
25										
26	Kracie Holdings, Ltd.	0 [0]	30,936 [209]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120
27										[698]
28										
29	GlaxoSmithKline K.K.	111,370 [754]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	111,370
30										[754]
31										
32	Minophagen Pharmaceutical Co.	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	110,440	0 [0]
33									[748]	[748]
34										
35	Maruho Co., Ltd.	0 [0]	103,120 [698]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	103,120
36										[698]
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5	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]
6											
7	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]
8											
9	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]
10											
11											
12	Horay Industries, Inc.	0 [0]	0 [0]	0 [0]	77,080 [522]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	77,080 [522]
13											
14											
15	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]
16											
17	Foyama 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]
18											
19	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]
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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

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5	Eisai Co., Ltd.	Eribulin	7.8	52.8	No	No	No	Yes	No	No	No	No	Yes
6													
7	Eli Lilly Japan K.K.	Pemetrexed	37.3	252.5	Yes	No	No	No	No	No	No	No	No
8													
9	Eli Lilly Japan K.K.	Ramucirumab	28.9	195.7	Yes	Yes	No	No	No	No	No	No	No
10													
11	Nippon Boehringer	Afatinib	8.7	58.9	Yes	No	No	No	No	No	No	No	No
12	Ingelheim Co., Ltd.												
13													
14	Novartis International	Imatinib	27.5	186.2	No	Yes	Yes	No	No	No	No	No	No
15	AG												
16													
17	Novartis International	Nilotinib	20.7	140.1	No	No	Yes	No	No	No	No	No	No
18	AG												
19													
20	Novartis International	Everolimus	15.1 [†]	102.2 [†]	Yes	Yes	No	Yes	Yes	No	Yes	No	No
21	AG												
22													
23	Ono Pharmaceutical	Nivolumab	103.9	703.5	Yes	No	Yes	No	Yes	No	Yes	Yes	No
24	Co., Ltd.												
25													
26	Daiho Pharmaceutical	Tegafur/Gimer	26.9	182.1	Yes	Yes	No	Yes	Yes	No	No	No	No
27	Co., Ltd.	acil/Oteracil											
28													
29	Daiho Pharmaceutical	nab-Paclitaxel	20.7	140.1	Yes	Yes	No	Yes	No	No	No	No	No
30	Co., Ltd.												
31													
32	Daiho Pharmaceutical	Calcium	9.7	65.7	No	Yes	No	No	No	No	No	No	No
33	Co., Ltd.	Folate											
34													
35	Daiho Pharmaceutical	Tegafur,	6.5	44.0	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
36	Co., Ltd.	Uracil											
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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

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5	Novartis Pharma K.K.	Ruxolitinib	September 24, 2015	Added indication	Polycythemia vera
6					
7	Novartis Pharma K.K.	Dabrafenib	March 28, 2016	New approval	Melanoma
8					
9	Novartis Pharma K.K.	Trametinib	March 28, 2016	New approval	Melanoma
10					
11	Novartis Pharma K.K.	Ceritinib	March 28, 2016	New approval	Non-small cell lung cancer
12					
13	Novartis Pharma K.K.	Everolimus	August 26, 2016	Added indication	Neuro-endocrine tumor
14					
15	Ono Pharmaceutical Co., Ltd.	Nivolumab	February 29, 2016	Added indication	Melanoma
16					
17	Ono Pharmaceutical Co., Ltd.	Nivolumab	December 17, 2015	Added indication	Non-small cell lung cancer
18					
19	Ono Pharmaceutical Co., Ltd.	Carfilzomib	July 4, 2016	New approval	Multiple myeloma
20					
21	Ono Pharmaceutical Co., Ltd.	Nivolumab	August 26, 2016	Added indication	Renal cell cancer
22					
23	Ono Pharmaceutical Co., Ltd.	Nivolumab	December 2, 2016	Added indication	Hodgkin lymphoma
24					
25	Ono Pharmaceutical Co., Ltd.	Nivolumab	March 24, 2017	Added indication	Head and neck cancer
26					
27	Otsuka Pharmaceutical Co., Ltd.	Ponatinib	September 28, 2016	New approval	Chronic myelogenous leukemia
28					
29					Multiple myeloma
30					Non-Hodgkin lymphoma
31	Sanofi K.K.	Plerixafor	December 19, 2016	New approval	Hodgkin
32					lymphoma
33					
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35					
36	Sanofi K.K.	Aflibercept Beta	March 30, 2017	New approval	Colorectal cancer
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5	Shionogi & Co., Ltd.	Cyclophosphamide	June 26, 2015	Added indication	Malignant lymphoma
6					
7	Shionogi & Co., Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
8					
9	Taiho Pharmaceutical Co., Ltd.	Trabectedin	September 28, 2015	New approval	Sarcoma
10					
11	Takeda Pharmaceutical Company Ltd.	Prednisolone	June 26, 2015	Added indication	Malignant lymphoma
12					
13					Prostate cancer
14	Takeda Pharmaceutical Company Ltd.	Leuprorelin	September 28, 2015	New approval	Breast cancer
15					
16	Takeda Pharmaceutical Company Ltd.	Ixazomib	March 30, 2017	New approval	Multiple myeloma
17					
18					
19	Yakult Honsha Company, Limited.	Oxaliplatin	November 20, 2015	Added indication	Gastric cancer
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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.