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Out-of-pocket costs sustained in the last 12 months by cancer patients: an Italian survey-based study on individual expenses between 2017 and 2018

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Abstract

Purpose Out of Pocket costs (OOP) sustained by cancer patients also in public NHS contribute to disease-related financial toxicity. Aim of the study was to investigate the amount and the types of OOP sustained by Italian cancer patients for care services.

Methods A sample survey was conducted by FAVO in December 2017-June 2018, in 39 adhering hospitals and 1289 patients diagnosed from 1985 to 2018, by standardized questionnaire inquiring on: yearly expenditure by cancer service, age, year of diagnosis, disease phase, cancer site, sex, marital status, education, residence. Univariate and multivariable regression analyses were performed between OOP and each variable. Multilevel mixed-effects negative binomial regression was used to assess the combined effects of patients characteristics on the differences in acquiring health services.

Results The yearly average OOP was 1841.81€, with the highest values for transports (359.34€) and for diagnostic examinations (259.82€). Significantly higher OOP were found in North and Centre than South and Islands (167.51 vs. 138.39). In the fully adjusted multivariable analysis, the variables significantly associated with higher than reference expenditure were: medium/high education (OR 1.22 [1.05–1.42], upper gastrointestinal tract cancer (OR 1.37 [1.06–1.77]), disease phase of treatments for cancer progression or pain therapy (OR 1.59 [1.30–1.93]).

Conclusion Italian cancer patients in 2018 sustained OOP quite similar to those measured in 2012 to supplement NHS services. The main component of the OOP costs were diagnostic examination and transportation. The NHS should pay attention to potentiate its ability to answer unmet needs of patients with advanced cancer who are the most fragile ones.

Implications for cancer survivors Reinforcing the services where the main OOP expenses are located can help in promoting public health actions and reduce socio-economic needs that could compromise the receipt of optimal care along the whole disease course, from diagnosis to rehabilitation.

Keywords Out-of-pocket health expenditures · Cancer patients · Cancer care · Financial toxicity · National health system

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Introduction

Financial toxicity has been largely recognized as a growing concern for cancer patients, first in the United States, where the health system is characterized by a prevalent role of private insurances, but subsequently involving other countries, particularly those with a low-middle income, including many with public health systems [1–8].

Out of Pockets (OOP) costs are a relevant aspect of the financial toxicity associated to cancer care, because it expresses both the financial burden sustained by the patients and their families and the mental distress, anxiety,

depression, impairment of quality of life, and long-term financial disadvantage associated to such economic aspect.

In 2012, in Italy, a first study on financial burden of cancer patients and their caregivers and on care, social and OOP costs was carried out by FAVO, National Cancer Institute of Milano and Censis (one of main Italian social research Foundation), through Italian Association of Cancer Patients (Aimac) information points set in major cancer Italian Institutes [9].

Such study included a majority of patients under anti-cancer treatment (1,055 patients) and 713 caregivers. It calculated that the social cost attributable to all patients and their caregivers was equal to 36.4 billion euros/year, of which over 5.8 billion were direct expenses (medical and non-medical, such as home helps, transport, hotel expenses, special diets, etc.) and over 30 billion were indirect costs. Of the latter, more than 12 billion (34%) were attributable to the surveillance and assistance activities directly provided by the caregiver.

Furthermore, the loss of sick people's income from work accounted for 10.5 billion (over 29%), while that for caregivers amounted to another 6.45 billion (17.7%).

Therefore the overall repercussions of the disease on labour determined a cost of almost 17 billion. The per-capita social cost for patients and their caregivers within the first two years after diagnosis was 36.1 thousand euros; in the timeframe between 2 and 5 years after diagnosis it was 30.7 thousand euros, and 34.2 thousand euros per year for the total patients for whom a maximum of 5 years had elapsed since diagnosis of cancer.

Subsequently, in 2016, we found a relevant financial burden in around one fourth of 3670 Italian cancer patients with lung or breast or ovarian cancer, enrolled in clinical trials of chemotherapy between 1996 and 2012; such financial hardship at baseline was predictive of worse outcome of treatment in terms of quality of life at the end of chemotherapy. In addition, patients who worsened their financial distress during chemotherapy also had a higher probability of death, with a hazard ratio of 1.20 (95% CI 1.05–1.37) as compared with those not worsening their financial condition during treatment [7]. These data derived from a retrospective evaluation of responses given by the patients to a question, included in the EORTC quality of life core questionnaire, that is quite generic and does not allow comprehension of determinants of financial distress [10].

For this reason, we produced a specific set of study parameters—the PRO instrument PROFFIT—that has been recently published [11–13].

Based on these past experiences, in 2018, FAVO performed a new survey to verify how the extent of the socio-welfare and health costs sustained by patients and their relatives after a cancer diagnosis had changed as compared with the 2012 findings. Specifically, we investigated the main types of OOP costs for care-related goods and services by geographic residence and patients' characteristics, to extend and update the findings of the 2016 paper by Baili et al. [9].

Materials and methods

Data collection procedures

The research was based on a sample survey whose data collection methodology consisted in a self and hetero administered individual questionnaire (i.e. administered by a professional interviewer or self-compiled by the patient, possibly helped by his/her caregiver, according to the will of the interviewed) [14] in a period from 15th December 2017 to 30th June 2018.

The survey was conducted by FAVO and carried out with the collaboration of the information points of Aimac. Data were collected by a standardized questionnaire, exploring the main aspects of the patient's coping with the disease, from diagnosis and therapies to economics, quality of life and social issues.

As the interviews were carried out during the visits in hospitals, our study population was mainly constituted by patients who were under treatment for primary cancer or in follow-up for tumour progression, metastasis, pain therapy. To construct a study sample representative of the whole Italian cancer population, we assumed that within two years since diagnosis most patients can be considered under treatment either for primary cancer and its consequences, or actively followed up. Based on this assumption, the percentage of 2-year prevalent cases was applied and re-proportioned to the total 3,304,648 prevalent cancer cases estimated in Italy for the year 2017: in descendent order of frequency those of colon-rectum, lung, breast, prostate and genitourinary system, upper gastrointestinal tract. The patient sample consisted of a minimum of 1170 interviews with a distribution of interviews that took into account the tumour site, the geographical area and the gender of the patient. The 1170 patients to be interviewed would allow a sampling error of 2.9% corresponding to a confidence level of 95%. The sampling design used the criterion of proportional allocation with respect to tumour sites and gender, introducing minimum sample size thresholds equal to 100 interviews for the most frequent tumour sites.. The location of the information points (IPs) guaranteed a broad coverage of the territory; in any case, in the phase of weighting to the estimated reference universe the sample was post stratified also by geographical area to analyse the cost estimates also by territory.

Finally, a total number of 1289 patients diagnosed in a period from 1985 to 2018 was interviewed, exceeding the expected quota sample. To assure an adequate representation

power (the quota sample is a not probabilistic one), the proportion of the main patients' characteristics (sex, age, tumour site) had to be preserved in the final number of interviewed people with respect to the same proportion in the total prevalent population considered for the study. A resume of the population number was reported in Supplementary Table S1.

The patients recruitment was carried out using the network of IPs of Aimac (39 IPs distributed in Italy). The questionnaire was administered at each IP issuing authorization by Aimac volunteers receiving adequate training on the objectives and technical and formal contents of the research, through a face to face interview of patients giving their consent.

The data extracted from the paper questionnaires were entered on an IT platform to allow activity monitoring and analysis. Volunteers were asked to administer the questionnaire to all currently treated patients and their caregivers available in the IP.

The volunteers were provided with a link to the online platform, accessed by a unique username and password for entering the questionnaires, so that each access corresponded to one questionnaire.

At each IP, the minimum objective was to collect one questionnaire per day for patient and one per day for caregiver, maintaining the distribution by tumour site. The individual information points began (and therefore concluded) the survey in different periods due to the different authorization times of the ethics committees.

The variables sex, age class and tumour site were periodically monitored, to preserve the proportion of these characteristics in the quota sample, as well as the progressive number of questionnaires by each IP.

The research was carried out in full compliance with the privacy regulations in force in the relative period of collection of the questionnaires (Legislative Decree 196/2003, subsequently Regulation No. 2016/679 GDPR). The data collected were processed and analysed in aggregate form so that it was not possible to trace the responses to the identity of the subject.

Questionnaire and variables characteristics

The questionnaire reported 38 questions grouped in six different conceptual areas: characteristics of the oncologic disease; current phase of the disease (considering only the last year before the interview); costs sustained by patients in the last year; psychological, relational and quality of life aspects; effects of the disease on the job position and condition; socio-demographic information.

Out-of-Pocket (OOP) costs related to cancer were considered and identified by asking patients or caregivers about the direct expenses they sustained, which were not covered or only partially covered by the NHS, for the following health-related goods and services: Diagnostic examinations; Specialist post-diagnosis examinations; Integration/support treatments; Post-diagnosis radiological tests, nuclear medicine, biological samples, others; Physiotherapeutic performances and rehabilitation; Reconstructive surgery; Health aids (prostheses, hairpieces, etc.); Medical devices (wheelchair, oxygen tank, etc.); Non-oncologic drugs; Special diet; Private nurse; Professional domestic worker/caregiver/home assistant; Transports; Rooms, accommodations, etc.; Psychotherapy/Psychological support; Other services. They were chosen for their relevance in the patterns of diagnosis, care and recovery in convalescence (or palliative support) from the neoplastic disease [9, 15].

Age was grouped into the following categories: < 60, 60–69, 70–79, and 80 + . Marital status was dichotomized as: married/cohabiting, unmarried/divorced/widowed. Education was dichotomized as low and medium/high level (i.e. the low level includes no qualification and elementary school diploma, whereas the medium–high level include junior school, high school, degree, and post-degree.

The years of diagnosis was classified in three groups: 1985–2012 (representing patient alive for more than five years from diagnosis), 2013–2016 (representing patient alive from five to one year from diagnosis), 2017–2018 (representing patient alive till to one year from diagnosis).

Disease phase was created by grouping patients in two categories: first therapeutic phase after diagnosis, subsequent treatments for cancer progression or pain therapy. This grouping considered the declaration of the patients about the care actions at the interview time. Cancer site was grouped as described above, considering that the interviewed patient or the corresponding care-giver identified the cancer site.

The patient characteristics were described considering the geographic macro-area of residence (North and Centre; South and Islands) [16].

Statistical analysis

Univariate and multivariate regression analyses were performed between OOP costs (outcome variable) and the variables identified a priori as potentially cost-related (independent variables): patient-related variables (age, sex, marital status, education level, area of residence, family structure), disease-related variables (year of diagnosis, cancer site, disease phase).

OOP costs were determined as the mean costs of all the patients who sustained such cost in the last 12 months before the interview. In the calculation of the cost averages and in the relative regression analyses, the 1123 respondents who gave a Yes or No answer to the question on whether or not they used a certain service were considered. The 166 non-responders were considered as missing values. In the

calculation of the OOP expenditure incurred, the cost of NHS prescription charge was excluded.

Also, the average monthly OOP cost for the individual characteristics were computed; the OOP expenses were considered excluding the health ticket.

The independent variables were chosen to maintain a comparability of the results with the 2016 article [9].

In the calculation of the cost averages and in the relative regression analyses, only the 1123 respondents who gave a Yes or No answer to the question of whether or not they used a specific service were considered.

In case patient had not incurred any medical expenditure, a zero value was inputted as cost; therefore, the cost-related outcome was a zero-inflated numerical variable, with a mix of zeros and positive continuous observations. According to our previous findings [9], with this type of outcome variable the classical ordinary least squares regression model could produce biassed results due to the combination of sample size with respect to the corresponding population [17] and the wide presence of zeros [18]. In synthesis, this kind of bias usually produce overestimated both Odds Ratios (ORs) and predicted values of the dependent variable.

Therefore, to find the most important cost predictors, we applied a multilevel mixed-effects negative binomial regression to define the combined effects of the individual characteristics and the area of residence on the differences in acquiring health services and goods by OOP.

All analyses were performed using STATA software version 14 (StataCorp LP, College Station, TX, USA).

Results

Table 1 reports the distribution of the characteristics of the interviewed patients and their cancer by geographic macro area of residence.

The IPs where interviews were carried out were slightly more present in Northern and Central Italy (58%, 742 interviews) than in Southern Italy and Islands (42%, 547 interviews), but the difference in terms of interviewed patients was not statistically significant ($p = 0.681$). Supplementary Table S2 shows the geographic distribution of the 1289 questionnaires by IP.

Women were more frequent in the North and Centre; married or cohabiting people and couples with sons in the South and Islands.

Colorectal and genito-urinary cancers were more frequent in the southern and islander patients; female breast, upper gastrointestinal tract along with other cancer sites in the northern and central ones; lung cancers were equally distributed.

The period of cancer diagnosis was more recent (2017–2018) in South and Islands, less recent (till to 2016) in North and Centre.

Regarding the goods and services bought by OOP, Tables 2 shows the distribution and the mean costs for every considered item.

Diagnostic examinations (51.4%) represented the main service responsible for OOP costs, followed by transports (45.1%), specialist post-diagnosis examinations (28.9%), non-oncologic drugs (28.5%), and accommodations (26.7%).

The highest OOP expenses were devoted to transports (359.34 euros on average), followed by diagnostic examinations (259.82 euros on average), accommodations (226.78 euros on average), reconstructive surgery (149.62 euros on average), and specialist post-diagnosis examinations (126.12 euros on average).

Morevorer, Table 3 shows some aspects of the unmet needs of the patients.

When asked about the areas of daily living that were more negatively affected by the tumour, patients mainly identified psychological issues in coping with the disease and its consequences. The difference with the other aspects was remarkable and statistically significant.

Family and activities of daily living were the second block of aspects relevant for the patients, whose difference with the other aspects was statistically significant.

Table 4 shows the monthly average OOP cost by patients' characteristics.

Area of residence was relevant, with higher OOP costs in the North and Centre than in South and Islands.

Education level influenced OOP with higher costs sustained by patients at medium/high qualification than those at low level.

With respect to disease characteristics, patients affected by upper gastrointestinal tract cancers sustained the highest OOP costs, and the category "Other cancer sites" was the second highest OOP cost.

Year of diagnosis influenced significantly the expenses, with higher costs in the 2013–2016 period than the others. At the moment of the interview (December 2017-June 2018), most patients diagnosed in 2013–2016 were between the first and fifth year after diagnosis, when most actions for care, support and recovery occurred. OOP costs were significantly higher in the phase of tumour progression and recurrence treatment, and pain therapy than the first therapeutic phase after diagnosis.

Table 5 shows the combined effects of the individual characteristics and the area of residence on the differences in acquiring health services and goods by OOP.

When all covariates are combined in one full adjusted model, education level, type of cancer and phase of disease remain statistically significant, with the odds of OOP

Table 1 Patients' characteristics by geographic area of residence

Variable	North and centre		South and Islands		Total	
	N	%	N	%	N	%
Sex						
M	228	32.9	236	39.6	464	36.0
F	465	67.1	360	60.4	825	64.0
Age class						
<60	346	50.4	279	48.9	625	49.7
60–69	192	28.0	170	29.8	362	28.8
70–79	123	17.9	100	17.5	223	17.7
≥80	25	3.6	22	3.85	47	3.74
Marital status						
Unmarried/Divorced/Widowed	239	34.5	140	23.5	379	29.4
Married/Cohabiting	454	65.5	456	76.5	910	70.6
Education level						
Low	316	45.6	287	48.2	603	46.8
Medium/High	377	54.4	309	51.9	686	53.2
Family number						
1-person family	127	18.3	62	10.4	189	14.7
Couple without sons	102	14.7	74	12.4	176	13.7
Couple with sons	372	53.7	404	67.8	776	60.2
Other composition	92	13.3	56	9.4	148	11.5
Cancer site						
Colon-rectum	52	7.5	82	13.8	134	10.4
Lung	77	11.1	67	11.2	144	11.2
Female breast	228	32.9	171	28.7	399	31
Upper gastrointestinal tract	112	16.2	74	12.4	186	14.4
Genitourinary cancers	80	11.5	99	16.6	179	13.9
Other cancer site	144	20.8	103	17.3	247	19.2
Year of diagnosis						
1985–2012	124	17.9	68	11.4	192	14.9
2013–2016	245	35.4	210	35.2	455	35.3
2017–2018	324	46.8	318	53.4	642	49.8
Disease phase						
First therapeutic phase after diagnosis	347	50.1	287	48.2	634	49.2
Recurrence treatment, tumour progression treatment, metastasis treatment, pain therapy	346	49.9	309	51.9	655	50.8

% denominator is the total number of interviewed cases (= 1289), except for the Age class variable, which is based on 1257 cases (32 missing cases). Tumours in the Upper gastrointestinal tract group: oesophagus, liver, pancreas, stomach, others. Tumours in the Genitourinary cancers group: ovary, prostate, kidney, testis, uterus, vagina, bladder, vulva, others. Tumours in the Other cancer site group: skin (not melanoma), pharynx, bones, haematological tumours, neuroendocrine system, central nervous system, soft tissues, thyroid, head & neck, oral cavity, others

remaining higher for patients with higher education, upper GI tract cancer and more advanced phase of treatment.

Also, the stochastic constant was statistically significant in increasing the OOP costs throughout the whole Italian patients, suggesting that other individual and disease characteristics should be considered.

Finally, also the information on job status was considered in the models described in Tables 4 and 5, but it was excluded because it did not pass the collinearity test.

Discussion

Three findings among those illustrated in this manuscript deserve discussion.

First, the composition of the OOP expenses.

The present study found that in Italy cancer patients spent on average more than 1800 euros annually.

The most frequent OOP component (around 260€ representing 14% of the overall OOP) was represented by

Table 2 Type of OOP costs by potential users (not users, paying/not paying users) and Average OOP costs for services

Type of OOP costs (no prescription charge)	Service not used		OOP paying users		Not OOP paying users		Average OOP costs	
	N	%	N	%	N	%	Mean cost (€)	Std. Dev
Transports	617	54.9	506	45.1	0	0.0	359.34	26.84
Diagnostic examinations	382	34.0	577	51.4	164	14.6	259.82	19.58
Rooms, accommodations, etc	823	73.3	300	26.7	0	0.0	226.78	24.97
Reconstructive surgery	1060	94.4	37	3.3	26	2.3	149.62	39.03
Specialist post-diagnosis examinations	624	55.6	325	28.9	174	15.5	126.12	11.62
Non-oncologic drugs	803	71.5	320	28.5	0	0.0	124.26	10.66
Health aids (prostheses, hairpieces, etc.)	917	81.7	204	18.2	2	0.2	122.22	18.40
Drugs related to non-oncologic comorbidities	834	74.3	254	22.6	35	3.1	113.58	19.86
Professional domestic worker/caregiver/home assistant	1054	93.9	69	6.1	0	0.0	84.27	17.84
Special diet	894	79.6	210	18.7	19	1.7	82.36	9.67
Post-diagnosis radiological tests, nuclear medicine, biological samples, others	700	62.3	195	17.4	228	20.3	63.94	8.74
Integration/support treatments	1063	94.7	52	4.6	8	0.7	42.67	9.59
Other services	1106	98.5	17	1.5	0	0.0	41.19	21.18
Private nurse	1063	94.7	60	5.3	0	0.0	24.87	4.61
Physiotherapeutic performances and rehabilitation	1060	94.4	43	3.8	20	1.8	17.78	3.93
Medical devices (wheelchair, oxygen tank, etc.)	1071	95.4	49	4.4	3	0.3	15.17	3.17
Psychotherapy/Psychological support	1111	98.9	12	1.1	0	0.0	7.62	2.76
Total OOP costs							1841.81	93.78

The % are computed on the basis of the total number of interviewed cases who declaring something about expenses (=1123). 166 cases were not considered in the analyses, because they did not declare anything about expenses. In the calculation of the cost averages and in the relative regression analyses, only the 1123 respondents who gave a Yes or No answer to the question of whether or not they used a specific service were considered. 166 cases who gave no answer were excluded

Table 3 Areas of daily living more negatively affected by the tumour diagnosis

Areas of suffering after tumour	N	%	95% Lower CI	95% Upper CI
Psychological aspects	736	57.1	54.4	59.8
Activities of daily living	642	49.8	47.1	52.5
Family	586	45.5	42.8	48.2
Occupation/Job position	437	33.9	31.4	36.5
Social relationships	435	33.8	31.2	36.4
Economic	415	32.2	29.7	34.8
Other aspects	51	4.0	3.0	5.2

CI Confidence interval (at 95%)

diagnostic examinations that were reported by more than half of patients (51.4%) largely exceeding the proportion of patients (14.6%) who reported that they received diagnostic examinations paid by the health system. Actually, diagnostic examinations if appropriate should be paid by the NHS and the high rate of patients who pay for diagnostic tests may be due either to inappropriateness of the diagnostic prescription or to inadequacy of public hospitals to provide diagnostic services on due time. This clearly represents a problem that needs to be highlighted, because even if the cost of diagnostic tests is much lower than that of therapeutic interventions, cancer patients requiring frequent restaging may accumulate a significant financial load if not adequately supported by the NHS. Clearly, more attention should also be paid to research on appropriateness of diagnostic tests, particularly during follow-up when their use is frequently considered matter of controversy [19].

The second most important component of the OOP is represented by transports, a problem that affects 45% of the patients in our study and explains almost 20% of the overall OOP. This finding is consistent with the fact that transportation is a theme represented by two items (dealing with distance from hospital and cost of travelling) classified as possible determinants of financial toxicity in the recently developed PROFFIT questionnaire (REF).

Table 4 OOP average monthly cost by patients' characteristics

Variables	Total			
	N	Mean cost (€)	Std. Dev	P (based on the Wald χ^2 of the model)
Area of residence				
North and Centre	**582**	**167.51**	**300.36**	**0.0116**
South and Islands	**541**	**138.39**	**212.15**	
Sex				
M	396	141.70	275.20	0.127
F	727	159.90	254.32	
Age class				
<60	549	166.89	287.37	0.0865
60–69	316	134.54	191.13	
70–79	191	164.35	301.73	
≥80	40	138.09	242.45	
Marital status				
Unmarried/Divorced/Widowed	321	146.43	233.12	0.4362
Married/Cohabiting	802	156.31	272.65	
Education level				
Low	**516**	**133.55**	**254.42**	**0.0013**
Medium/High	**607**	**170.43**	**267.12**	
Family number				
1-person family	155	145.31	241.49	0.8311
Couple without sons	155	165.67	241.72	
Couple with sons	689	152.38	278.80	
Other composition	124	154.62	210.79	
Cancer site				
Colon-Rectum	**114**	**121.13**	**196.83**	**0.0057**
Lung	**130**	**137.32**	**226.72**	
Female breast	**352**	**140.12**	**222.94**	
Upper gastrointestinal tract	**162**	**196.81**	**293.76**	
Genitourinary cancers	**159**	**143.15**	**247.17**	
Other cancer sites	**206**	**178.33**	**344.24**	
Year of diagnosis				
1985–2012	**151**	**159.83**	**271.95**	**0.0399**
2013–2016	**398**	**171.34**	**292.45**	
2017–2018	**574**	**139.44**	**235.07**	
Disease phase				
First therapeutic phase after diagnosis	**554**	**121.94**	**187.77**	**0.0000**
Subsequent treatments for cancer progression or pain therapy	**569**	**184.20**	**315.03**	

No missing cases were considered in the computation of means and univariate negative binomial regression model, therefore the total number of cases for every single variable may vary. Prescription charges were not included; transport expenses were included. Tumours in the Upper gastrointestinal tract group: oesophagus, liver, pancreas, stomach, others. Tumours in the Genitourinary cancers group: ovary, prostate, kidney, testis, uterus, vagina, bladder, vulva, others. Tumours in the Other cancer site group: skin (not melanoma), pharynx, bones, haematological tumours, neuroendocrine system, central nervous system, soft tissues, thyroid, head & neck, oral cavity, others

Bold characters remark the statistic significance ($p < 0.05$)

Clearly, strategies to allow cancer patients be treated as close as possible to their residency should be implemented and regional network may be crucial to warrant proximity of cure. Also, implementation of telemedicine procedures might represent a useful tool to reduce troubles derived from transportation expenses [20].

Second, the association of higher OOP with higher education level.

Table 5 Combined effects of the individual characteristics on the differences in acquiring health services and goods by OOP

Variables	OR	95%-CI Lower limit	95%-CI Upper limit	P
Area of residence				
North and Centre	1			0.195
South and Islands	0.90	0.78	1.05	
Sex				
M	1			0.184
F	1.14	0.94	1.37	
Age class				
< 60	1			0.404
60–69	0.84	0.70	1.01	
70–79	1.03	0.83	1.27	
≥ 80	0.81	0.54	1.23	
Marital status				
Unmarried/Divorced/Widowed	1			0.095
Married/Cohabiting	1.32	0.95	1.82	
Education level				
Low	**1**			**0.010**
Medium/High	**1.22**	**1.05**	**1.42**	
Family number				
1-person family	1			0.569
Couple without sons	0.94	0.62	1.42	
Couple with sons	0.87	0.60	1.26	
Other composition	1.11	0.82	1.51	
Cancer site				
Colon-Rectum	0.91	0.67	1.23	**0.040**
Lung	1.09	0.81	1.46	
Female breast	**1**			
Upper gastrointestinal tract	**1.37**	**1.06**	**1.77**	
Genitourinary cancers	1.02	0.80	1.32	
Other cancer sites	**1.28**	**1.01**	**1.63**	
Year of diagnosis				
1985–2012	1			0.534
2013–2016	1.06	0.83	1.35	
2017–2018	1.12	0.85	1.46	
Disease phase				
First therapeutic phase after diagnosis	**1**			
Subsequent treatments for cancer progression or pain therapy	**1.59**	**1.30**	**1.93**	0.000
Constant	81.21	54.04	122.05	0.000

P (based on the Wald χ^2 of the model) = 0.0000 (the model is statistically significant)

Due to the presence of missing cases, 1096 cases were considered in the total model: 578 cases for the North and Centre model, 518 cases for the South and Islands model. Prescription charges were not included; transport expenses were included. Tumours in the Upper gastrointestinal tract group: oesophagus, liver, pancreas, stomach, others. Tumours in the Genitourinary cancers group: ovary, prostate, kidney, testis, uterus, vagina, bladder, vulva, others. Tumours in the Other cancer site group: skin (not melanoma), pharynx, bones, haematological tumours, neuroendocrine system, central nervous system, soft tissues, thyroid, head & neck, oral cavity, others

Bold characters remark the statistic significance ($p < 0.05$)

This association remains statistically significant at multivariable analysis and may indicate a composite phenomenon that links higher education with a higher socio-economic status, living in the North of Italy and being exposed to a larger offer of private health solutions, that are much less present in the South of the country. This consideration is

strengthen by observing the connection between education level and self-declared income class: it is statistical significant (χ^2 test, statistical significance threshold at $p < 0.05$), with income growing at education level increase and a more frequent presence of higher education titles in the North and Centre of Italy than in the South.

Another consideration is relevant: patients with higher education level (and higher income) better cope with higher OOP in terms of financial toxicity; on the contrary, the expenses for the same services for patients with lower education level (and corresponding lower income) can be a too consistent burden to bear, pushing them to the waivers of such services.

This phenomenon is less critical if it is based on a higher willingness to pay to increase comfort during cancer treatment rather than on the need to pay OOP to obtain the due assistance. From this point of view, having identified the suffering for psychological issues (and, secondly, for the worsening of the management of the family relationships and the activities of daily living) as relevant needs that do not cause relevant OOP expenses should suggest that they are unmet needs not adequately covered by the National Public Health System and that only the most affluent part of the patients could afford.

As a confirmation, another analysis on this data has shown that patients at lower income (mainly corresponding to lower education) are more inclined to forego services requiring OOP and which could compromise the patients'/families' economic condition, the main services in descending order being: professional domestic worker/caregiver/home assistant, health aids (prostheses, hairpieces, etc.), reconstructive surgery, diagnostic examinations, physiotherapeutic performances and rehabilitation, transports (complete data not shown). These findings strengthen the above consideration that some relevant needs of the care pattern, particularly after the acute phase but very relevant for health and quality of life recovering, are not adequately meet by the National Public Health System.

Such situation significantly contributes to increase disparities among patients characterized by different economic condition, not justifiable in presence of a universalistic public health system.

Much more relevant is the third finding, that is the association of higher OOP with more advanced disease. This association too remains significant at multivariable analysis and represents a severe alarm, because it affects the most fragile and vulnerable population of patients, those living with an advanced cancer, most probably no longer amenable to curative treatment but candidate to chronic palliative treatment that may also last for several years thanks to therapeutic progress. Clearly, intensity of cure and unmet needs are higher in this population and the NHS should be more ready to satisfy such needs. Particularly,

health services organization and collaboration among health care providers should be focussed to make easier the journey of patients that require frequent accesses to the hospital, assume many drugs both anticancer or to treat symptoms and side effects, and are particularly unable to cope with bureaucracy, waiting lists and other troubles that may affect the quality of the NHS response. Again, the same themes were selected during the development of PROFFIT as potential determinants of financial toxicity [11–13].

It is interesting that no significant differences in expenditure were found during the years of study: the OOP costs throughout the whole Italian patients remained constant, or slightly decreasing. This constancy seems to be in contrast with the general increase in health expenditure, in particular for oncology. It could be explained by an improvement in the coverage and organization of health services, which therefore would not make it necessary to increase patients' OOP expenses. But it could also be due to patients' lower spending power, due to the financial toxicity of the disease, and in this case it would represent a higher degree of hardship.

OOP expenses are also documented in other countries with total or partial national health coverage. For instance, a Chinese multicentre study based on a cross-sectional survey [21] indicated that medical insurance protects some households with breast cancer patients from the impact of catastrophic health expenditure. However, their reimbursement rates were relatively low. Therefore, breast cancer still had a significant catastrophic effect on the economy of households.

More generally, a 2016 UK study [22] found that the economic burden of cancer survivorship was unevenly distributed in the population and that cancer survivors may still incur substantial costs over one year post-diagnosis, thus confirming some of the results presented above.

Finally, a 2019 Finnish study [23] started from the hypothesis that financial difficulties experienced by cancer patients may affect their Health-Related Quality of Life (HRQoL). The study assessed the direct economic burden that out-of-pocket (OOP) payments cause and explored how they and financial difficulties are associated with HRQoL. The results is in line with our findings: the highest OOP payments were caused by outpatient medication. Total costs and OOP payments were highest in the palliative care group in which the OOP payments consisted mostly of outpatient medication and public sector specialist care. Private sector health care was an important item of OOP payments in the early stages of cancer. Financial difficulties increased together with OOP payments. HRQoL deteriorated the more a person had financial difficulties. High OOP payments are related to financial difficulties, which have a negative effect on HRQoL. Outpatient medication was a major driver of OOP payments. Among palliative patients, the economic burden was highest and associated with impaired HRQoL.

Conclusion

Italian cancer patients and their families or caregivers spend about 1800 euros yearly to supplement services that are totally in charge to the NHS. Such OOP expenses measured in 2018 were quite similar to those measured in 2012. The main component of the OOP costs were diagnostic examination and transportation, indicating that the NHS should focus on increasing its ability to provide appropriate diagnostic examination and possibility of cure as closer is possible to the place where patients live. Also, the NHS should pay attention to potentiate its ability to answer unmet needs of patients with more advanced cancer who are the most fragile ones.

Declarations

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