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Forgotten public health impacts of cancer – an overview

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Cancer is one of the diseases of greatest concern in developed countries and much effort has been invested in discovering and developing therapeutics for curing cancer. Despite the improvements in antineoplastic therapeutics in the last decades, cancer is still one of the most harmful diseases worldwide. The global burden of cancer also implies financial costs: these can be direct costs, such as those related to treatment, care, and rehabilitation and indirect, which include the loss of economic output due to missed work (morbidity costs) and premature death (mortality costs). There are also hidden costs such as health insurance premiums and nonmedical expenses that are worth noting. This paper intends to present an overview of the generally forgotten impacts that the increasing number of cancer cases can have on the environment, workers who handle antineoplastic drugs, and health services. The knowledge available of each of the impacts will be addressed and discussed regarding the expected development. Overall, lessons learnt reflect on the impact of cancer through aspects not commonly evidenced in the literature or even considered in socio-economic analysis, in part due to the fact that these are difficult to contemplate in direct and indirect cancer costs already defined. Attention may be drawn to the need of continuous investment in prevention to reduce the negative impact on the environment, and in the health of workers who handle antineoplastic drugs for patients' treatment.

KEY WORDS: *costs of cancer; global burden; occupational health*

Globally, cancer is a growing public health problem. It is the second cause of death (21 %) after cardiovascular diseases (48 %), followed by respiratory diseases (12 %) in the sector of non-communicable diseases or diseases caused by non-infectious and non-transmissible medical conditions (1). Important resources are mobilised in order to improve research on new therapeutics, and ultimately devise a cure for this particular disease. Despite the increase in the effectiveness and specificity of chemotherapeutic treatments, cancer still remains one of the most harmful diseases (2-4).

In 2012, worldwide incidence of cancer rose to an estimated 14 million new cases per year, with an estimated 8.2 million cancer deaths. The most common cancers diagnosed were of lung (1.8 million cases, 13 %), breast (1.7 million, 11.9 %) and colon (1.4 million, 9.7 %) (1). Some of these numbers can be partially due to environmental exposure to carcinogens. In 2003, Boffetta and Nyberg (5) stated that despite the relatively small relative risks of cancer resulting from exposure to environmental carcinogens, the number of cases that might be caused, assuming a causal relationship, is relatively large due to the high prevalence of exposure. Regarding occupational cancer numbers, every year more than 100 000 people die from cancer related with exposure occurring in the workplace (6-8).

The majority of these cancers are caused by exposure to chemical substances. All of these cases could be avoided by eliminating the presence of carcinogenic substances in workplaces through alternative means of production including substitution of chemicals, by a systematic implementation of preventative measures and by an organisation of work that aims to avoid contact with carcinogenic substances (9).

A study conducted by Rushton and colleagues (10) intended to estimate the current burden due to past occupational exposure for six types of cancers, including lung cancer. It was possible to conclude that asbestos contributed with over half of the occupational attributable deaths, followed by silica, diesel engine exhaust, radon, work as a painter, mineral oils in metal workers and in the printing industry, environmental tobacco smoke (non-smokers), work as a welder, and dioxins. Despite asbestos being one of the most relevant causal agents for occupational lung cancer deaths registered until now, its banning has resulted in the reduction of cases only in some countries where the use of asbestos was reduced earlier. Most of the projections for industrialised countries still suggest that asbestos related diseases (including cancer) will continue to increase for many years to come (11). Additionally, the use of asbestos is increasing in many developing countries

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and some numbers suggest that exposure may still be high in those countries (12). This example demonstrates how important it is to eliminate the use of carcinogenic substances in all consumers' products as to avoid their presence in workplaces. This should be a common world effort and in this way it would be possible to prevent some countries, with more fragile economies, having to deal with this burden.

Workplace is not the only way of exposure to carcinogens: food intake and environmental pollution can have an important role as well (13, 14). Given the abovementioned, preventing exposure to carcinogens could reduce cancer incidence. The global burden of cancer is accompanied by a financial load, including direct costs, such as treatment and rehabilitation costs, and indirect costs, related to productivity losses due to absenteeism, disability, and premature death. Hidden costs of cancer also comprise health insurance premiums and nonmedical expenses (15, 16).

Although the exact global financial burden of cancer is unknown, in 2011, in the United States of America, the estimated direct medical costs for cancer were $88.7 billion (15). In 2009, in Europe, cancer costs amounted to €126 billion, with health care accounting for €51.0 billion (40 %), at a €102 cost *per* person, varying from €184 *per* person in Luxembourg to €16 *per* person in Bulgaria. Productivity losses due to early death cost €42.6 billion and €9.43 billion is due to lost working days (17). This research also concluded that the highest economic burden was related to lung cancer (€18.8 billion, 15 % of overall cancer costs), followed by breast cancer (€15.0 billion, 12 %), colorectal cancer (€13.1 billion, 10 %), and prostate cancer (€8.43 billion, 7 %). Moreover, the American Cancer Society (15) declares that the global cost of cancer is expected to rise due to an increase in the number of new cancer cases, as well as in the cost of cancer therapies.

It is also important to refer to some costs normally forgotten, probably due to the difficulty in assigning these a number. Examples of these are the impact on the environment and in the occupational context, the impact on the health of workers who handle antineoplastic drugs. Additionally, the need to reorganise health services to provide a better treatment of the increasing number of cancer patients should be considered. This is essential since, nowadays, socio-economic analyses performed in some cases to justify the use, and consequently exposure to a carcinogenic agent, consider only the costs arising from cancer mortality and morbidity, which results, in some cases, in an overestimation of the benefits. For instance, in the scope of European regulations, the well-known REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) supports a socio-economic analysis, weighing up the pros and cons of an action for society as a whole and plays a vital role in the restriction and authorisation processes for chemicals classified as carcinogenic, mutagenic, or toxic to reproduction. Both processes need a description of the risks as well as information on the health and environmental benefits, the associated costs and other socio-economic impacts (18). However, the only costs considered are essentially related with cancer mortality and morbidity.

Given the abovementioned, this review article aims to provide an overview of these generally overlooked impacts drawing attention to the costs that should be included in the overall decision-making on a carcinogenic agent's specific use (such as industrial chemicals), as well as the real scenario of use and exposure *versus* benefit for the society. In that manner, a review of published and grey literature was conducted, with incidence on the impact that the increasing number of cancer cases can have on the environment, workers who handle antineoplastic drugs, and in health services. To accomplish this, a thorough search was made for papers, other documents, and guidelines available in scientific databases and other relevant sources related with occupational exposure to antineoplastic drugs and also regarding the presence of these drugs in the environmental setting.

Antineoplastic drugs in cancer treatment

Responsible for many advances in therapy during the past century, chemicals have a successful history in the treatment of illnesses and injuries, and cancer is not an exception. Many drugs with diverse modes of action have been synthesised and adapted for clinical use. Antineoplastic or cytostatic drugs are a heterogeneous group of widely used therapeutics for neoplastic and non-neoplastic diseases. However, these drugs have been proved to be also mutagens, carcinogens, and teratogens (19-25).

Antineoplastic drugs include alkylating agents (e.g. cyclophosphamide, melphalan, chlorambucil, cisplatin), antimetabolites (e.g., thioguanine, 5-fluorouracil, methotrexate), antibiotics (e.g. doxorubicin), mitotic spindle inhibitors (e.g. vincristine), hormones (e.g. diethylstilbestrol), free radical generators (e.g. bleomycin) and topoisomerase inhibitors (e.g. irinotecan, etoposide) (26-29). There are also several so called "new generation" antineoplastic drugs that should be taken into account as well, such as taxanes (e.g. docetaxel), camptothecin analogues (e.g. irinotecan), thymidylate synthase inhibitors (e.g. raltitrexed), nucleoside analogues (e.g. gemcitabine), and protein kinase inhibitors (e.g., imatinib mesylate) developed for targeted chemotherapy (30-32).

In general, chemicals that interact directly with DNA by binding covalently or by intercalating, or indirectly by interfering with DNA synthesis, were among the first chemotherapeutics developed (33). Compounds that inhibit the mitotic spindle formation and those that affect the endocrine function are also used in cancer chemotherapy (34). Also, these drugs can induce reactive oxygen species that can lead to DNA damage and mutations, and consequently to cell death (35). It has to be pointed out that

these drugs are often used in combination, in order to achieve additive and/or synergistic effects on tumour cells resulting from their differing modes of action. However, most, if not all, of these chemical agents are generally non-selective and along with tumour cells, normal cells may undergo cyto/genotoxic damage (26, 36-39).

The *in vivo* exposure to antineoplastic drugs has been shown to induce different types of lesions in DNA, according to the inherent mechanism of action and also depending on the particular stage of cell cycle at the time of treatment. The majority of lesions occur during DNA synthesis, often due to misreplication. Both neoplastic and normal cells attempt to repair them. However, if unrepaired, DNA lesions may give rise to chromosome aberrations, which are able to interfere with the transcription and replication of DNA, resulting in cytotoxic and mutagenic effects. Due to all these characteristics, growing evidence suggests that secondary neoplasms may arise as a consequence of chemotherapy (37, 40-43).

Antineoplastic drugs impact on the environment

Cancer incidence has increased in the so-called "modern societies" in the last years, and so has the use of antineoplastic drugs (2). Because of this, the amount of such drugs, their metabolites and transformation products in the environment is of great concern since they may induce adverse effects on both the environment and human health. A particular emphasis has been put on the impact on the aquatic environment (24, 44-52).

Antineoplastic drugs commonly used in chemotherapy treatment enter wastewater trough sewage treatment plants and through excretion of the non-metabolised drug following its administration to patients. However, despite the increasing number of cancer patients, these drugs have received minor attention, considering their high pharmacological potency, foetotoxic, genotoxic, and teratogenic properties, which may well induce genetic and cell cycle alterations in aquatic fauna and flora if there is chronic exposure (51, 53, 54). The concern with these substances derives from their presence in freshwater systems and the consequent contamination of the potable water supply, with risk of human exposure (51, 54). Some authors state that, due to the continual input into the aquatic compartment, these drugs should be considered "pseudo"-persistent pollutants (50, 55, 56).

Some of these drugs are not completely metabolised and are poorly biodegradable. They can also be resistant to conventional biological and chemical processes used during wastewater treatment (53) and may represent a challenge for the state-of-the-art technologies of water decontamination (2, 48). Due to higher analytical sensibility to antineoplastic drugs, some of these chemicals have been reported in hospital waste effluents, in sewage treatment plants, and river water. A growing interest in this topic has been verified and data have been published in several studies (57-62).

Given that many of the drugs have similar pharmacology, it is possible to consider that they may act additively and/or synergistically once they enter the environment, possibly increasing their overall cytotoxicity, and consequently, the risk to aquatic organisms (51-63). Even if the concentration of one drug is low, the effect of a mixture might be of ecotoxicological importance (39, 64-66).

On this matter, recent studies have revealed that mixtures of anticancer drugs in real samples present an important toxicological effect when compared with an individual drug (67). For instance, a recent research work developed by Eleršek and colleagues (50) revealed that a low concentration of 5-fluorouracil, imatinib mesylate, and etoposide mixture had additive and/or synergistic effects on the growth inhibition of green algae and cyanobacteria. Also, in mixtures, the same toxic effect as induced by single instances of exposure was obtained at much lower concentrations of each single compound, meaning that lower concentrations in mixtures present the same toxicity as a higher single dose (50). Similar effects were observed when testing binary mixtures of selected antineoplastic drugs also on green algae and cyanobacteria indicating that mixtures can have compound-specific and species-specific synergistic or antagonistic effects (68). Authors concluded that single compound toxicity data are not sufficient to predict the aquatic toxicities of such antineoplastic drug mixtures. Moreover, in zebrafish liver cells, a mixture of cyclophosphamide, 5-fluorouracil, ifosfamide, and cisplatin was tested at maximal detected concentrations of each drug as determined in the effluents from the oncological ward. The tested mixture was not cytotoxic and did not induce genomic instability, but it induced a significant increase in DNA strand breaks at concentrations of individual compounds that were several orders of magnitude lower than those that were effective when tested as individual compounds. The authors concluded that such mixtures of anticancer drugs may pose a threat to aquatic organisms at environmentally relevant concentrations and contribute to the accumulating evidence that it is not always possible to predict adverse effects of complex mixtures based on the toxicological data for individual compounds (69).

Although concentrations of antineoplastic drugs in the aquatic environment could be below detection limits, they can reach alarming levels in biota through bioaccumulation and biomagnification processes. Hence, their impact should be carefully investigated since unexpected delayed effects on the offspring generations could be a matter of concern. In that manner, Kovacs and colleagues (70) investigated potential threats from low, environmentally relevant, concentrations of 5-fluorouracil using a two-generation toxicity study design with zebrafish (*Danio rerio*). Exposure of zebrafish to a selected antineoplastic drug was initiated with adult F0 generation and continued through the hatchings and adults of the F1 generation, and the hatchings of the F2 generation. Results indicated that even exposure to low concentrations of antineoplastic drugs might affect

fish populations over long-term exposure of several generations, which suggests that further studies into multi-generation toxicity are warranted.

Additionally, some studies state that there is still a lack of research on antineoplastic agents, their metabolites and transformation products, as well as on environmental fate and impact (2, 51). A fraction of these drugs is metabolised before being excreted and future studies should focus on the screening of metabolites and transformation products (which could also be present in wastewaters) since most of these compounds can have equal or even greater activity than the parent compounds (2, 71, 72).

Finally, it is important to bear in mind that the problem is not only focused in hospitals' wastewater as these drugs are also administered in outpatient clinics. Therefore, the release of antineoplastic drugs is very diffuse in the environment and difficult to control (51). Besides addressing solutions to treat hospital effluent "on-site" (before being discharged into the urban sewage collection system), management of human excretions (urine and faeces) from oncologic patients as a separate form of waste with potential environmental impact needs to be studied. Antineoplastic agents must be considered a group of new and emerging environmental pollutants, which can produce impact on aquatic life, wastewater treatment plants and water receiving effluents and in that manner, more data on the occurrence and effects of such pollutants are needed to enable efficient environmental risk assessment (2, 73).

Occupational exposure to antineoplastic drugs

According to the European Guidelines (74), any use of carcinogenic, mutagenic or teratogenic substances, including the application in health care settings, is assigned to the highest risk level (20-23, 75). Based on epidemiological reports, animal carcinogenicity data, and the outcomes of *in vitro* genotoxicity studies, several antineoplastic drugs have been classified by the International Agency for Research on Cancer (IARC) as belonging to the group of human carcinogens (Group 1), probable human carcinogens (Group 2A), or possible human carcinogens (Group 2B) (76, 77).

Many anticancer agents have the potential to cause genetic alterations, which may lead to the development of cancer if they interact with proto-oncogenes or tumour suppressor genes, which are involved in controlling cell growth or differentiation (78). Exposure to any genotoxic agents may initiate a sequence of events that leads to adverse health effects. Although the potential therapeutic benefits of hazardous drugs outweigh the risks of side effects for ill patients, exposed health care workers risk these same side effects with no therapeutic benefit.

Along with the increasing number of cancer patients, a higher number of workers are potentially needed to handle production and administration tasks relative to antineoplastic drugs. In Portugal, for instance, since 2007 there has been no substantial recruitment of pharmacy professionals in order to follow the number of patients who need chemotherapy care. Also, the centralisation of cytotoxic production reduced it to five public health institutions, and the increased demand for these drugs forced teams to work in shifts (79), with relocation of professionals from other sectors of the hospital pharmacy to the cytotoxic oncology area.

Workers may be exposed to a drug at different stages of its life cycle – from manufacture to transport and distribution, during its use in health care or home care settings, or at its final waste disposal. Health care workers who prepare or administer hazardous drugs or who work in areas where they are used may be exposed to these agents in the air, on work surfaces, contaminated clothing, medical equipment, patient excreta, and other surfaces (80-83). These workers include shipping and receiving personnel, pharmacists and pharmacy technicians, nursing personnel, and environmental services personnel (20). Workers employed in the synthesis and production of these products and staff involved in cleaning, transport, and disposal of hazardous drugs or contaminated material may all face health risks (20, 36, 84-86). A study done by Meijster and colleagues (84) discussed the most important occupational settings outside hospitals in the Netherlands, where exposure to antineoplastic can also occur. Settings such as home care, nursing homes, and laundry facilities are the ones identified with higher exposure and are all related with probable care of cancer patients.

The biological effects may vary depending on the drug(s), its dose, and individual genetic susceptibility (80), but it is difficult to assess how much drug is absorbed in the course of handling agents at the workplace. The main focus of concern has dwelled upon the pharmacy and nursing personnel who mix and administer drugs and who are likely to experience the highest exposure intensity (87). Inhalation and skin contact/absorption are the most likely routes of exposure, but unintentional ingestion from hand to mouth contact and unintentional exposure from a needle is also possible (80, 82, 83, 88, 89). Inhalation results from aerosolisation of powder or liquid during reconstitution and spillage taking place while preparing or administering to patients; skin contact or skin absorption results from contact with contaminated surfaces mostly when control measures are inadequate. This type of exposure seems to have the most important role in dermal absorption (20, 79, 90, 91).

Contaminated food or cigarettes, but also hand contact with contaminated equipment used in preparing and administering these drugs, can lead to oral ingestion. Furthermore, patients may excrete these drugs and their metabolic by-products in body wastes, exposing personnel who handle such items (80, 89). Contamination of workplace surfaces and permeation of gloves to some antineoplastic drugs were reported already in several studies (22, 79, 80, 92).

The National Institute for Occupational Safety and Health (NIOSH) in the USA has compiled several case studies that suggest both acute and long-term health effects associated with antineoplastic drug occupational exposure scenarios. Various studies have associated workplace exposure with health effects such as skin rashes, hair loss, irritation, hypersensitivity, and headaches after reported skin contact (28, 93-96). Negative reproductive health outcomes are also associated with antineoplastic exposure (93, 97, 98). Spontaneous abortions have been reported approximately twice more often among exposed pregnancies than unexposed ones (94); the same goes for congenital malformations, infertility, and possibly leukaemia, as well as other cancers (80, 94, 99).

Health care workers handling antineoplastic drugs usually implement collective and individual protective measures. However, contamination of the work environment is still possible and the safety measures employed can be insufficient to prevent exposure (9, 100, 101). Even when strict protocols and standard operating procedures have been applied, studies reported the presence of widespread surface contamination (79, 102).

In a hospital setting, exposure to several antineoplastic drugs occurs simultaneously. The effects of such mixtures, at cell level and on human health in general, are unpredictable and unique due to the differences in the practice of hospital oncology departments, in the number of patients, protection devices available, and the experience and safety procedures of health professionals that handle these drugs (39, 66, 80, 103, 104). The growing use of complex mixtures of known and new antineoplastic drugs in cancer treatment emphasises concerns about occupational exposure and genotoxic risks of workers handling such mixtures. The presence of drugs in different amounts and with different mechanisms of action suggests the need to study the relationship between the presence of genotoxic components in the mixture and the ensuing effects, taking into account the mechanism of action of each component *per se* (39, 66, 105).

Presently, the concern also includes long-term risks of handling monoclonal antibodies (MABs), which were introduced into clinical practice in the mid-1980s, with their use in the healthcare setting increasing over the past decade. MABs have become established in the treatment of a variety of disease states including cancer, rheumatoid arthritis, transplanted organ rejection, psoriasis, and asthma. This group is more selective for cancer cells, and manufacturers have minimal data on the possible long term risks of handling MABs predominantly because they are not required to provide this information for licensing purposes (106-108).

Evolution of cancer care units

As already mentioned, several studies have been conducted to assess the financial burden of cancer. One the one hand, the financial burden of cancer, despite being high, is comparable or lower in comparison with that of other chronic diseases; for example, the burden of mental health and circulatory system is higher than that of cancer (109, 110). On the other hand, however, the burden of cancer has been increasing over the recent years, related to the increasing incidence, survival, and life expectancy of survivors, as well as the emergence of new therapies with extremely high costs (111).

All these studies on the cancer financial burden have appraised direct costs, which mainly consist of the costs of cancer treatments, and several studies have also evaluated indirect costs, mainly represented by productivity losses due to treatments, morbidity, and premature death. Yet, the increasing use of chemotherapy has prompted hospitals to reorganise their services in order to adapt to the most up-to-date way of providing cancer care. This reorganisation started in the 1990s and has been on-going since then, driven by the will to adapt services to new patient management procedures. We consider that this regular need for reorganisation represents an additional burden of cancer, which has rarely been addressed in the literature.

We briefly discuss here the shift from inpatient to outpatient care and the implementation of multi-disciplinary teams. Guidelines published in 1996 clearly mentioned the shift in the administration of chemotherapy from hospitalisation towards outpatient settings, which may be the hospital outpatient facilities or the oncologist's office (112). The advantages of care delivery as outpatient are listed in these guidelines, mainly referring to the easier way of administering drugs; the patient preferences (outpatient care provides more comfort and psychological well-being than inpatient settings); lower and better monitoring of costs; and greater flexibility of schedules. This shift towards outpatient settings was also driven by the pressure from hospital administrations and third-party payers to reduce expenditures and to free inpatient beds for competing needs (113). In practice, treatment is provided by skilled nurses over a few hours, using central venous access catheters, under the supervision of an oncologist immediately available to answer questions, revise medications, or intervene in case of a problem (112).

Outpatient therapy is now common for solid tumours but has also been adopted more recently for other more complex treatments; for example, high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT), and in the allogeneic non-myeloablative HSCT (113). In addition to previous arguments, the use of outpatient settings was also driven in this case by the long waiting time for inpatient care leading to delays in treatment. Savoie and colleagues (113) demonstrated that outpatient care was safe and feasible for these more aggressive treatments. These results confirm the findings of earlier studies, which showed that outpatient high-dose chemotherapy and autologous stem cell transplantation are efficient, effective, and acceptable (114, 115). More recently even, the challenge of shifting towards

outpatient care has been raised for other cancers, also with favourable outcomes: the treatment by vincristine, dactinomycin, and cyclophosphamide for children with solid tumours, as outpatient instead of the traditional two-day inpatient stay, has proven safe, cheaper, and more satisfactory for the patient (116); outpatient delivery of chemotherapy for acute lymphoblastic leukaemia/lymphoma was safe and not associated with increased toxicity as compared to inpatient delivery (117); outpatient management after chemotherapy for adults with acute myeloid leukaemia or myelodysplastic syndrome reduced costs and use of IV antibiotics (118). In other terms, the administration of chemotherapy in outpatient settings produces comparable outcomes while increasing patients' satisfaction and reducing costs.

However, this evolution in the management of chemotherapy raises serious challenges, which require additional precautions and higher expenditures. In particular, as compared to inpatient delivery, outpatient chemotherapy is performed over a shorter period of time, with a higher volume of interventions, and a lower level of control. The risks are higher if one considers lower continuity, self-administration of medications, and occurrence of side effects at home; a 3 % rate of medical errors was measured in a study. As the authors mention, the higher risk of error needs to be counteracted by commitment to error reduction and a culture of safety, including a computerised clinical decision support system, which is used at the different stages of care pathways by a multi-disciplinary team (119).

In the meantime, cancer therapies have rapidly become more efficacious and diverse but with an increasing complexity for professionals to select the optimal management plan. As mentioned by Fleissig and colleagues (120), there is thus a higher need for coordination and communication between health professionals and patients, which a multi-disciplinary team (MDT) can fulfil. The MDTs have various expected benefits, which Fleissig and colleagues (120) have detailed: better coordination of care (permitting more consistent information to patients and more efficient and simplified processes); greater continuity of care; better communication between professionals and with patients; better clinical outcomes (mostly because teams involving various skills and knowledge are more likely to opt for the most adequate management plan); and higher satisfaction and well-being of patients and health professionals (essentially because of the supportive environment).

Similarly to the shift towards outpatient care, the implementation of MDTs is challenging and requires commitment, support, and funding. The adequate functioning of MDTs requires leadership, administrative dedicated support to ensure the coordination, time and conditions for regular meetings, and larger well-financed teams (120). These requirements may be difficult to fulfil under adverse circumstances, such as budget pressure, hierarchical boundaries, insufficient staff, or historical and cultural barriers between health professions and services.

New cancer therapies have dramatically improved clinical outcomes; the efficacy and efficiency of cancer management, however, are likely to be enhanced under adequate and innovative organisation of cancer care units, involving in particular outpatient delivery and MTDs. These new forms of managing cancer care are, however, potentially difficult to implement and a strong commitment and additional funding are required. These are part of the hidden costs of cancer care, although these costs are very likely to be compensated in the long run by efficiency gains.

CONCLUSION

This paper reflects on the impact of cancer through aspects not commonly evidenced in the literature or even considered in socio-economic analysis, in part due to the fact that these are difficult to contemplate in direct and indirect cancer costs already defined. Three important impacts resulting from cancer are presented: antineoplastic relationship with the environment, the health of workers, and new organisation of health facilities. Considering this, attention may be drawn to the need of continuous investment in prevention, search for alternatives to substitute carcinogenic agents in industrial uses, thus reducing the negative impact on the environment, and in the health of workers who handle antineoplastic drugs for patients' treatment. Additionally, cancer prevention investment will allow health care units to better address patients' needs, focusing on diseases where prevention has a limited or null impact.

Conflict of interest

None declared.

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Zaboravljeni učinci raka na javno zdravstvo – pregled

Rak je jedan od najvećih problema javnog zdravstva diljem svijeta. To je jedna od najproblematičnijih bolesti u razvijenim zemljama te je dosta napora uloženo u otkrivanje i razvoj lijekova za liječenje raka. Unatoč razvoju antineoplastičnih lijekova u proteklim desetljećima, rak je i dalje jedna od najštetnijih bolesti na globalnoj razini. Globalno opterećenje raka uključuje i financijske troškove: može se raditi o izravnim troškovima poput onih vezanih uz liječenje, njegu i rehabilitaciju te o neizravnima, koji uključuju gubitak ekonomskih rezultata zbog izostanka s posla (troškovi morbiditeta) i prerane smrti (troškovi smrti). Tu su i skriveni troškovi poput premija zdravstvenog osiguranja i nemedicinskih troškova, koje isto tako valja istaknuti. U radu je dan pregled općenito zaboravljenih učinaka rastućeg broja slučajeva oboljenja od raka na okoliš, na zaposlenike koji rukuju antineoplastičnim lijekovima i na zdravstvene službe. Velika je pozornost posvećena postojećemu znanju o svakom pojedinačnom utjecaju te je razrađen očekivani razvoj navedenih učinaka. Općenito, prikazan je utjecaj raka kroz aspekte koji se uobičajeno ne dokumentiraju u literaturi niti razmatraju u socioekonomskim analizama, a djelomično je razlog tomu što ih je teško razmotriti unutar već definiranih izravnih i neizravnih troškova. Pozornost valja posvetiti i potrebi trajnoga ulaganja u prevenciju kako bi se smanjio negativan učinak na okoliš i na zaposlenike koji rukuju antineoplastičnim lijekovima.

KLJUČNE RIJEČI**:** *globalno opterećenje; troškovi raka; zdravlje na radu*