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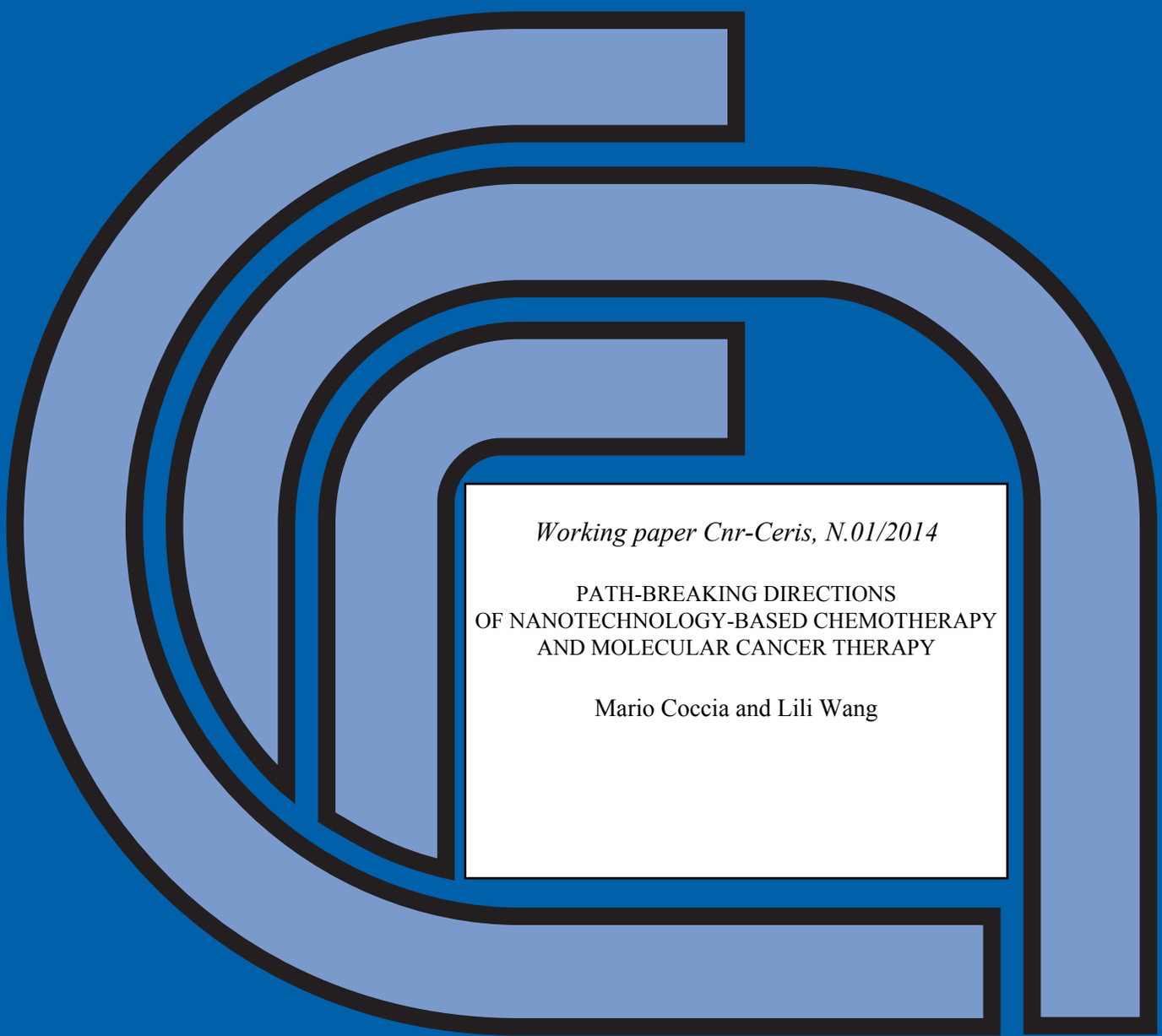

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PATH-BREAKING DIRECTIONS OF NANOTECHNOLOGY-BASED CHEMOTHERAPY AND MOLECULAR CANCER THERAPY

Mario Coccia and Lili Wang

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Path-breaking directions of nanotechnology-based chemotherapy and molecular cancer therapy

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ABSTRACT: A fundamental question is how to detect likely successful anticancer treatments based on nanotechnology. We confront this question here by analyzing the trajectories of nanotechnologies applied to path-breaking cancer treatments, which endeavour to pinpoint ground-breaking and fruitful directions in nanomedicine. Results tend to show two main technological waves of cancer treatments by nanotechnology applications. The early technological wave in the early 2000s was embodied in some types of chemotherapy agents with a broad spectrum, while after 2006, the second technological wave appeared with new nano-technological applications in both chemotherapy agents and molecular target therapy. The present study shows new directions of nanotechnology-based chemotherapy and -molecular cancer therapy in new treatments for breast, lung, brain and colon cancers. A main finding of this study is the recognition that, since the late 2000s, the sharp increase of several technological trajectories of nanotechnologies and anticancer drugs seems to be driven by high rates of mortality of some types of cancers (*e.g.* pancreatic and brain ones) in order to find more effectiveness anticancer therapies that increase the survival of patients. The study here also shows that worldwide leader countries in these vital research fields and in particular the specialization of some countries in applications of nanotechnology to treat specific cancer (*e.g.* Switzerland in prostate cancer, Japan in colon, China in ovarian and Greece in pancreatic cancer). These ground-breaking technological trajectories are paving new directions in biomedicine and generating a revolution in clinical practice that may lead to more effective anticancer treatments in a not-too-distant future.

Keywords: Nanotechnology, Nanoscience, Biomedicine, Nanomedicine, Target Therapy, Chemotherapy, Cancer, Bibliometrics, Publications, Technological Trajectories.

JEL Codes: C89; O30, C53, I10

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CONTENTS

1. INTRODUCTION AND THE PROBLEM

Interdisciplinary theoretical and experimental results related to nanoscience and nanotechnology in the life sciences are supporting the diagnosis, monitoring, prevention and treatment of diseases. Nanotechnology in medicine has generated a vital technological change and as a consequence a revolution in clinical practice (Islam and Miyazaki, 2010; Rafols and Meyer, 2010; Coccia, 2012a; Wolinsky *et al.*, 2012; Madeira *et al.*, 2013)[1]. No and Park (2010), using patent citations, argue that the interaction of biotechnology and nanotechnology may provide important signals for future patterns in nano-biomedicine (*cf.* Sylvester and Bowman, 2010; Coccia, 2012). In fact, nanotechnology has a high potential of development for biomedical purposes such as the ground-breaking applications in new therapies for oncology (*cf.* Lim *et al.*, 2010; Coccia, 2012a; 2012b).

Bibliometrics is an important approach for investigating emerging fields of nanotechnology (Arora *et al.*, 2013).

In fact, some studies, based on publications, show that the patterns of nanotechnology research are spreading among different scientific domains and pathways, generating new technological paradigms mainly in chemistry, medicine and engineering research fields (*cf.* Coccia, 2012a; Robinson *et al.*, 2013).

As far as the performance in nanotechnology research is concerned, Shapira and Wang (2010) show the leadership of some countries, such as the US and China, which are considered among the top nanotechnology research publishing countries.

This result can be due to high R&D investments in this vital research field and incentives given to researchers to publish in Web of Science indexed journals (Lin and Zhang, 2007; Shapira and Wang, 2009). However, Youtie *et al.* (2008) claim that publication counts do not necessarily equate to publication influence.

An interesting problem that deserves to be analyzed is how to detect the path-breaking directions of nanotechnology trajectories applied for vital anti-cancer treatments. In particular, we confront this main issue by analyzing:

- the directions of technological trajectories of the most common anticancer drugs (chemotherapy agents, substances, or target therapies) inserted in nanoparticle to treat cancers with more effectiveness;
- the evolutionary pathways of types of cancer where there is a high intensive research activity of treatments that use nanotechnology;
- the countries that are best performers in applications of nanotechnologies to treat cancer and the specialization of countries to treat specific cancer by nanotechnology.

This study can provide important information concerning emerging and fruitful directions of nanotechnology applied in ground-breaking anti-cancer treatments that may generate a revolution in clinical practice to improve human health and quality of life in a not-too-distant future.

[1] *cf. also* Genet *et al.*, 2012; Chen *et al.*, 2013; Tierney *et al.*, 2013, von Raesfeld *et al.*, 2012.

2. THEORETICAL BACKGROUND AND RELATED WORKS

Breakthroughs in nanotechnology are providing "a new dimension" to medicine (da Rocha *et al*., 2014). Therapies integrated in nanoparticles or cooperative nanosystems are spurring new insights to groundbreaking cancer treatments. The strategy of the National Cancer Institute with nanotechnology started in 2004 to support multidisciplinary researchers in the applications of nanotechnology to new anti-cancer treatments (Hull *et al.*, 2013). In fact, R&D in this field has experienced an exponential growth since the early 2000's, such that "cancer nanotherapeutics are progressing at a steady rate" (Bertrand *et al.*, 2013). For this reason, pharmaceutical companies have formed strategic alliances and partnerships with biotechnology firms to improve and accelerate the drug discovery process (Coccia, 2014a).

A fundamental question in the field of the economics of innovation is *how* trajectories of scientific fields evolve, expand, converge (or diverge) and break out. Bibliometrics plays a main role to detect and map this continuous evolution (Huang *et al.*, 2014), being associated with powerful software to analyze diverse and large volume of data. Motoyama and Eisler (2011, p. 1174) consider bibliometrics the "primary method of gaging progress in nanotechnology". As a matter of fact, social scientists, more and more, use bibliometric and scientometric approaches to detect and analyse trajectories in the wide domain of cancer nanotechnology research (Wang *et al.*, 2013).

These approaches play an important role to explore the current evolutionary knowledge growth of trajectories of nanotechnology that may support future patterns of technological innovation in emerging and cutting-edge areas of biomedical sciences. De Bellis (2009) observes that citation analysis, a bibliometric technique, is a prominent feature in the study of new scientific knowledge.

Thomas *et al.* (2011) discuss a nanoparticle ontology for cancer nanotechnology research to represent knowledge underlying nanomaterials involved in cancer research. Huang *et al.* (2010) show that there are different search strategies for nanotechnology research such as citation analyses, core journal strategies (core is when the journal has nano in its title), lexical queries, etc. (*cf.* Mogoutov and Kahane, 2007). Zitt *et al.* (2011) argue that keywords act as main signals of scientific inquiry, while citations are more effective in identifying research streams. Using a keyword mining approach, Wang *et al.* (2013) find that the general trend of integration in the application of nanotechnology fields is converging.

Arora *et al.* (2013) employ structured text-mining software to profile keyword terms and identify new nanotechnology-related keywords. This strategy shows the main role of several emerging cited-subject categories of nanotechnology, particularly in the biomedical sciences. Instead, Zitt and Bassecoulard (2006) employ citation networks to expand their corpus of nanotechnology publications. Leydesdorff and Zhou (2007) present an approach based on a core set of six nanotechnology journals and citation and network analysis to provide fruitful results in understanding this research field.

Among all the research areas, biomedicine is one of the key scientific fields where nanotechnologies are providing vital

innovative applications in diagnostics and in therapeutics (*cf.* Hu *et al.*, 2011; da Rocha *et al.*, 2014; Gao *et al.*, 2013). Coccia (2012a) displays that the current convergence of genetics, genomics and nanotechnology is the scientific backbones of new technological paradigms and trajectories in biomedical sciences. This convergence of vital scientific fields is supporting innovative anticancer treatments and a revolution in clinical practice.

There are several nanotechnologies applied in biomedicine for supporting anti-cancer treatments (Chen *et al.*, 2011; He *et al.* 2010; Luo *et al.*, 2011). For instance, Nanoparticles (NPs) can be designed to selectively target the specific tissue/organ in which there is the cancer (Coccia, 2012b).

In addition, functionalizing the surface of NPs with specific and appropriate ligands can allow their use as drug carriers to target them selectively to the tissue/organ affected by cancer (*see* Pöselt *et al.*, 2012; Shukoor *et al.*, 2012; Shukoor *et al.*, 2011). Nanoparticles can also act as carriers for drugs, which can be contained into organic nanomicelles or porous inorganic nanoparticles that, by apt bioactive systems, can target tumoral cells of the body (*see* Yao *et al.*, 2011; Goel *et al.*, 2010).

Quantum Dots (QDs), instead, are a specific subset of NPs (Obonyo *et al.*, 2010; Byers and Hitchman, 2011; Rosenthal *et al.*, 2011). The QDs in medicine are mainly applied as targeted drug delivery (Jain, 2012).

Carbon nanotubes are an allotropic form of carbon, having cylindrical structure and can be used to deliver drugs against cancer cells, protecting them towards external agents (Ezzati Nazhad Dolatabadi *et al.*, 2011; Bareket *et al.*, 2010). In fact, carbon nanotubes combined with cytotoxic (antineoplastic or chemotherapy) agents are a key area of development for biomedical sciences (Shapira *et al.*, 2011).

Some edge areas of bio-nano-medical applications (closer to molecular biology) are still at the stage of first experimental trials, such as the combination between nanoparticle and siRNA[2].

Gao *et al.* (2013) show that nanomedicine, based on a targeted drug delivery system, significantly improve cancer metastasis treatments.

Hence, nanotechnology-based approaches are a promising research field for early-stage diagnosis and for advanced treatments of cancers that have high rate of mortality (Patra and Truner, 2014; Coccia 2014; Coccia, 2013; 2012c).

GLOBOCAN (2008) shows high mortality (in terms of Age-standardized rate[3]), in comparison to incidence, by cancer of the lung and bronchus (19.3), breast (12.4), colorectum (8.2), cervix uteri (7.8), prostate (7.4), ovary (3.8), pancreas (3.7) and brain (2.5).

[2] Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA molecules that play a variety of roles in biology.

[3] *Mortality*: Population weighted average of the area-specific country rates applied to the 2008 area population.

Age-standardised rate (W): A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardised rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer.

In general, these serious diseases can be treated with:

a) Chemotherapy agents that are cytotoxic anti-neoplastic drugs to destroy cancer cells;

b) Targeted cancer therapies that are: "drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression" (National cancer institute as quoted by Coccia, 2012b, p. 276);

c) Antiestrogen therapy, such as tamoxifen, that blocks the effects of the hormone estrogen in the breast;

d) Cancer siRNA therapy (SiRNA seem to substantially better than antibodies, because they might easily applicable to any therapeutic target including intracellular factors and even transcription factors. The selectivity of siRNA inhibitors of gene expression might improve targeted cancer therapeutics, but the means for systemic administration and targeted distribution to disseminated metastatic lesions are needed; *see* Schiffelers *et al.*, 2004);

e) Chemopreventive substances, such as curcumin.

We confront the initial problems of the paper by analyzing the evolution and fruitful directions of trajectories of the nanotechnology applied to improve these different types of treatments for above-mentioned cancers with higher rate of mortality.

3. METHOD OF RESEARCH

We analyse evolution and direction of the most important and ground-breaking anticancer treatments based on:

- Nanotechnology with chemotherapy agents (cytotoxic anti-neoplastic drugs) such as Paclitaxel, Cisplatin, Gemcitabine, Carboplatin, Docetaxel, Doxorubicin, etc.;
- Nanotechnology with molecular cancer therapies such as herceptin, cetuximab, lapatinib, tamoxifen (antiestrogen), and cancer *si*-RNA therapy;
- Nanotechnology with chemoprevention substances such as curcumin.

Considering the high mortality of some types of cancer discussed in the previous section, seven cancer fields - brain cancer, breast cancer, colon cancer, lung cancer, ovarian cancer, pancreatic cancer and prostate cancer – are covered in our analysis.

The performance of this paper is based on a set of publication and citation data collected from Scopus in the 2013. The search query was developed by the combination of nano and each cancer field, searched from abstracts, keywords and titles. The time span covers 13 years (2000-2012). Research records prior to 2000 were not included because of insignificant publication numbers. To refine the data quality, we excluded publications that appeared in less relevant sources, *e.g.* journals in social science, etc., but we focus on 12 important journal categories[4]. In total, this

[4] These 12 journal categories are: 1) Medicine, 2) Biochemistry, Genetics and Molecular Biology, 3) Pharmacology, Toxicology and Pharmaceutics, 4) Health Professions, 5) Nursing, 6) Engineering, 7) Chemistry, 8) Agricultural and Biological Sciences, 9) Immunology and Microbiology, 10) Neuroscience, 11) Chemical Engineering, 12) Materials Science.

study covers 5,080 (nano & cancer treatment) publications, including 1,440 cited references from nanotechnology. VantagePoint and Ucinet software are used for accurate and deeper analysis as well as for visualizing technological networks.

After gathering all the publication records, we classify the applications of nanotechnology into different groups by keywords. We focus on vital types of anticancer drugs/therapies applied by means of nanotechnology.

The nanotechnology and anticancer drug groups are: 01) nano & paclitaxel, 02) nano & cisplatin, 03) nano & gemcitabine, 04) nano & carboplatin, 05) nano & docetaxel; 06) nano & doxorubicin, 07) nano & herceptin (or trastuzumab), 08) nano & lapatinib, 09) nano & Cetuximab, 10) nano & tamoxifen, 11) nano & siRNA and 12) nano & curcumin[5]. In particular, No. 01-No. 06 are new anti-cancer treatments based on chemotherapy agents applied by nanotechnology, while target therapies applied with nanotechnology are No.07, 08, 09; antiestrogen therapy (Tamoxifen) applied by nanotechnology is No. 10; cancer siRNA therapy is No. 11 and chemoprevention substance is No. 12.

Some technological fields, such as: 13) nano & EGFR (or epidermal)[6], 14) nano & HER2 (or HER-2), 15) nano & RNA, 16) nano & PLGA (poly lactic glycolic acid)[7], which also provide substantial information about ground-breaking applications of cancer treatments *via* nanotechnology, are included while gathering our publication database. However, due to the fact that they do not represent anticancer drugs, they are not illustrated in the technology-specific analysis.

The study is conducted by the following steps:

- *Step 1*: To examine the evolutionary growth of nanotechnology applied in cancer research. From the perspective of target fields, the evolutionary development of nanotechnology applied in cancer treatment field are mapped.
- *Step 2*: From the perspective of applied nanotechnology, the vital role of nanotechnology applied with some anticancer treatments is explored by citation analysis.
- *Step 3*: To link (within a *network*) specific nanotechnology and anticancer drugs with a specific cancer field.

Remark: Some evolutionary trends are plotted by a Log-Linear Regression model[8], estimated by Ordinary Least Squares Method in order to approximately measure and assess, by the coefficient of regression, the acceleration of some technological trajectories.

[5] Number 13, 14, 15 and 16 are not included in the figures in next section, because these keywords do not concern anticancer drugs but EGFR (epidermal growth factor receptor: the protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide.), HER2 (a protein involved in normal cell growth), etc.

[6] For EGFR and HER2, *see* previous footnote.

[7] Poly(lactic-co-glycolic acid) (PLGA) is one of the most successfully developed biodegradable polymers. Among the different polymers developed to formulate polymeric nanoparticles, PLGA has attracted considerable attention due to its attractive properties (Danhier F. *et al.*, 2012).

[8] The estimation of a linear relationship is based on the following model: $\text{Log}Y_i=\alpha+\beta T_i+\varepsilon_i$; $i=1, \ldots, n$ (T_i=*Time*; ε_i=Errors).

Given that not all the nanotechnologies are equally applied in all cancer treatments, we adopt network analysis to link and detect the specific nanotechnology and anticancer drugs/therapies to cancer field.

- *Step 4*: To spot the top profile countries which are in the leading position in applying new cancer treatments by nanotechnology.

Moreover if we suppose *i* is a certain country and *j* is the cancer field, the research weight of country *i* in field *j* can be calculated by *i*-country's publications in *j*-field divided by all global publications in *j*-field. Hence, the general research weight index (θ_i) of *i*-country is the sum of *i*-country's research weight in all cancer fields. This is given by:

$$\theta_i = \sum_{j=1}^{n} \frac{Publications_{ij}}{Publications\ worldwide_j} \quad (1)$$

- *Step 5*: To examine the internal specification of each top country.

Each country may have their own concentration of research in nanotechnology applied to treat specific types of cancer. Therefore, we use the following index to examine country's specialization in the seven cancer treatment areas. Specialization ratio of country *i* in field *j*, defined as C_{ij}, is the ratio of its publications in *j* field divided by its total publications in all cancer fields.

Specialization ratio of worldwide in *j* field, written as W_{ij}, is the ratio of worldwide publications in *j* field divided by total publication in all cancer fields worldwide. The disparity between C_{ij} and W_{ij} is the specialization index of country *i* in field *j*, which is taken as γ_{ij} .

$$C_{ij} = \frac{Publications_{ij}}{Total\ Publications_i}; \quad j = 1, \dots, n. \quad (2)$$

$$W_j = \frac{Total\ Publications\ j}{Publications\ Worldwide}; \ \text{j=1,…,n} \quad (3)$$

$$\gamma_{ij} = C_{ij} - W_j; \quad j = 1, \dots, n. \quad (4)$$

A high level of index γ_{ij} indicates that the high specialization of the country *i* in the specific research field *j*. In particular, $\gamma>0$ means high specialization in the scientific research in this type of cancer, whereas if $\gamma < 0$ means that there is lower specialization. High values γ means a higher intensive research activity in the specific cancer area by application of nanotechnology to cancer treatments. In addition, this study intends to test the following hypothesis (HP) by a hypothetical-deductive approach *à la* Carl Hempel:

HP: *High growth of trajectories of nanotechnology applied to new anticancer treatments is due to higher rate of mortality of some types of cancer.*

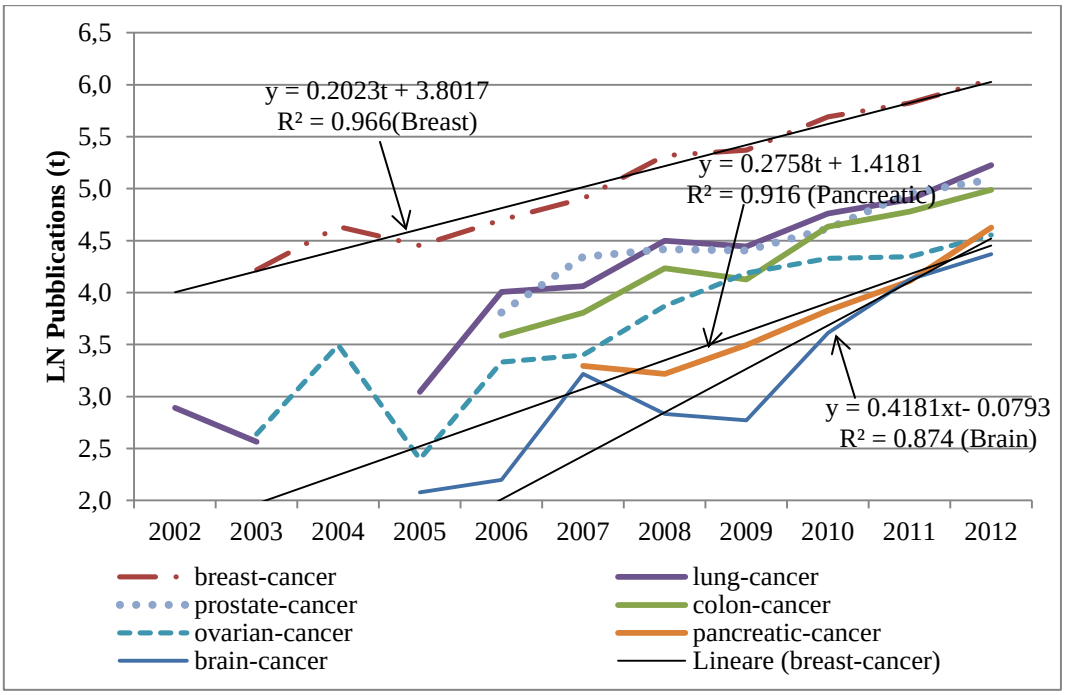
In order to validate this HP, a main statistical technique applied is the nonparametric measure of association by the coefficients of correlation Tau-b of Kendall and of Spearman between average nano-citations and ratio mortality/incidence. This research departs from the position that there can be no adequate knowledge where causes are unknown and analyses the phenomena to be explained by a scientific realism.

4. EXPERIMENTAL RESULTS AND DISCUSSIONS

Figure 1 shows that the number of scientific publications concerning cancer treatments associated to nanotechnology is growing over years. The highest magnitude of scientific output in these research fields is driven by cancers that have a high incidence rate, such as breast, lung and colon cancer. In addition, it is interesting to note that growth rate of scientific research by brain and pancreatic cancer is increased sharply in later years, although they had a low activity of scientific production in early 2000. In fact, coefficient of regression (a proxy of increase over time) by brain and pancreatic cancer trends is higher than Breast cancer. In the long run, there shows a convergence of these trajectories over time. This general trend can be further approved by the citation of nanotechnology in these fields (*see* Figure 1A in Appendix).

To take the size of different research fields into account, we calculate the average of nano citation intensity concerning nano applications in the studied seven cancer fields. In particular, Table 1 shows that nanotechnology applications have the highest citation intensity in brain cancer. Following brain cancer, pancreatic cancer is the second field where nanotechnology has been intensively applied to new anticancer treatments, with average nano-citation intensity at 11.9%.

Albeit the total research output of nanotechnology in breast cancer, colon cancer and prostate cancer, as showed in Figure 1, is rather high, the citation intensity of nanotechnology in these three cancer fields is relatively low (*see* the last three rows of the first column in Table 1).



Note: The logarithm of publications is taken to better present the values. This figure also shows the estimate relationships by ordinary least square (and R square) to indicate approximate rate of growth of some trends.
Source: Authors' own calculation.

Figure 1: Publications of cancer treatments by nanotechnology in different typology of cancer (2000-2012)

Table 1: Intensity of nano citation (standardized) and mortality ratio in cancer field

Field	Average of nano citation intensity in cancer field (average of 2009-2012)	RaMI=Ratio of Mortality/incidence
Brain-cancer	19.3%	0.714
Pancreatic-cancer	11.9%	0.949
Ovarian-cancer	8.7%	0.603
Lung-cancer	8.3%	0.843
Breast-cancer	8.1%	0.319
Colon-cancer	6.8%	0.477
Prostate-cancer	6.8%	0.265
Coefficients of Correlation between average nano-citations and ratio τ are: Tau-b of Kendall= +0.59; Spearman =+0.76 (*sig*. 0.05)		

Note: 1) The percentage of nano citation is standardized. Namely, the citation intensity is calculated by the citation of nano in that year divided by the total publications of that cancer field in all previous years.
2) Due to the lack of citation data for some small research fields in early years, the average is taken between 2009 and 2012.
Source: Authors' own calculation.

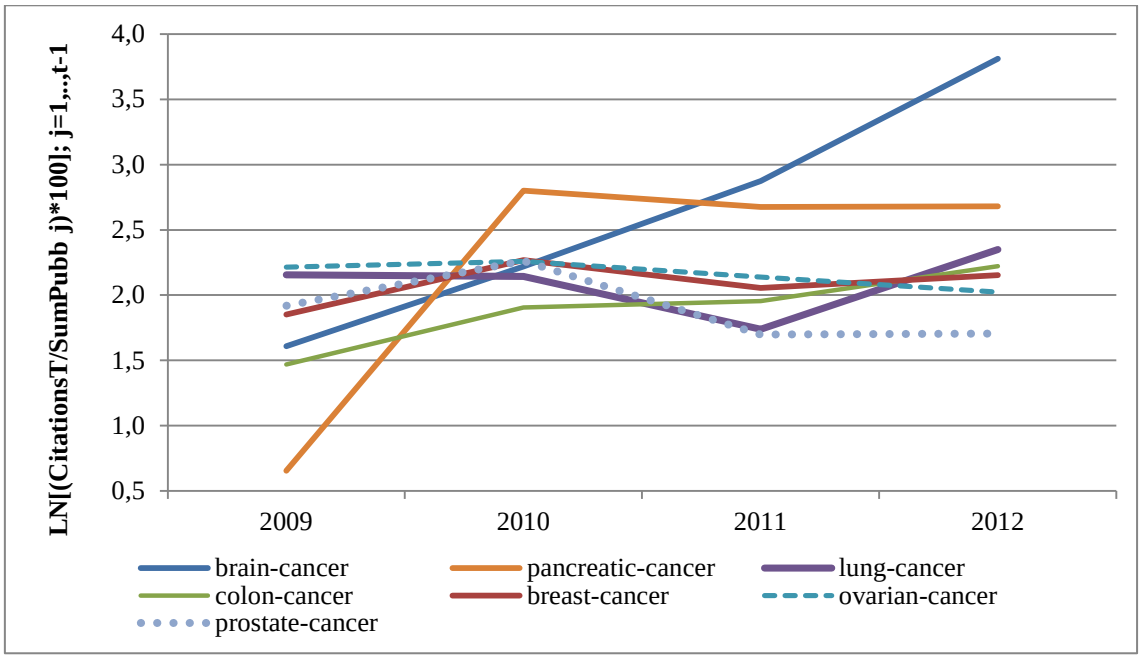
In order to test the HP, Table 1 shows the combination of factors of the mortality and incidence rate of different cancer fields.

It is interesting to observe that cancer fields in which the Ratio of Mortality to Incidence (Called RaMI) is high, all have high nano citation density, and *vice versa*.

In fact, coefficients of correlation between average nano-citations and ratio RaMI are: Tau-b of Kendall= +0.59; Spearman =+0.76 (sig. 0.05). This result suggests that cancer fields, where incidence is low while mortality is high, although the total joint research output with nanotechnology is relatively low, the intensity of nanotechnology applications to ground-breaking anticancer treatments is very high.

This reveals that nanotechnology plays a crucial role in these specific cancers (with high mortality rate) because it might support new technological avenues to find effective therapies in order to increase the survival of patients.

This result validates the HP and is confirmed by Figure 2, where the high intensive citations of nanotechnology research are exactly in brain and pancreatic cancer (*cf.* also the Figure 1A).



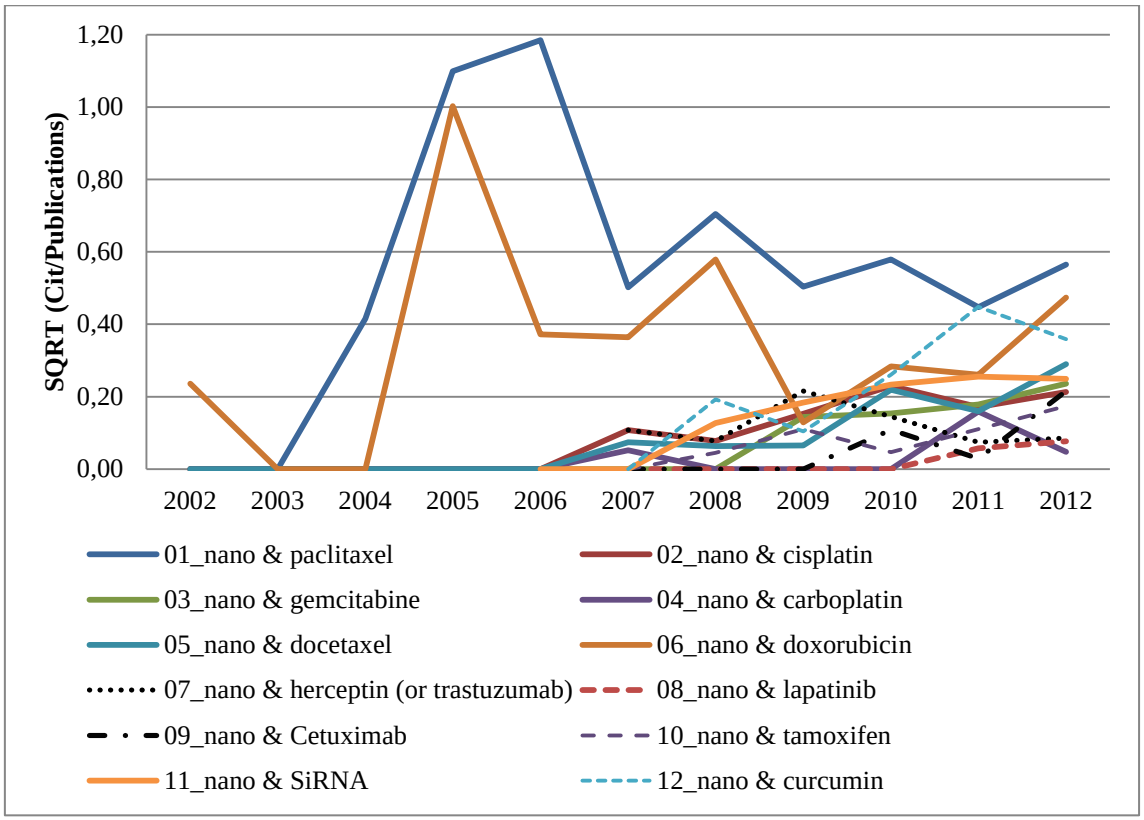
Note: The logarithm of publications is taken to better present the values.

Source: Authors' own calculation.

Figure 2: Citation intensity of nanotechnology in cancer fields per different typology of cancer (2009-2012)

Figure 3 shows the trajectories of main anticancer drugs applied by nanotechnology. This figure displays interesting findings. First of all, the scientific research of chemotherapy agents applied through nanotechnologies is started in 2002-2003 (*i.e.* No.01 - No.06), whereas the new molecular target therapies leveraged with nanotechnologies are started later, 2007 or thereabouts (No. 07, 08, 09, 10, 11, 12). As a matter of fact, since 2002 the highest intensity of scientific research in new anticancer treatments is based on well-know chemotherapy agent paclitaxel (discovered in US during 1960s) and doxorubicin (discovered in Italy over 1950s) with nanotechnology. The high growth of these anticancer drugs can be due to broad spectrum of applications to treat different cancer: Doxorubicin is commonly used to treat some leukemias and Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and others. Instead, paclitaxel albumin-stabilized nanoparticle formulation is a form of paclitaxel contained in nanoparticles (very tiny particles of protein). This form seems to work better than other forms of paclitaxel and has fewer side effects. National Cancer Institute (2013) states that paclitaxel albumin-stabilized nanoparticle formulation is approved to be used alone or with other drugs to treat:

- Breast cancer that has recurred (come back) or metastasized (spread to other parts of the body).
- Non-small cell lung cancer that is locally advanced or has metastasized and cannot be treated with surgery or radiation therapy. It is used with carboplatin.
- Pancreatic cancer that has metastasized. It is used with gemcitabine hydrochloride.



Note:1) Chemotherapy agents applied with nanotechnologies are No. 01-No.06, while molecular target therapies and other anticancer treatments are No.07-No.12.
2) No.13-No.16 are not included in this figure because they do not concern anticancer drugs but EGFR, HER2, etc.
3) Square root is applied to better represent the values.
Source: Authors' own calculation.

Figure 3: Main nanotechnology streams associated to drugs to treat the cancers (2000-2012)

Paclitaxel albumin-stabilized nanoparticle formulation is also being studied in the treatment of other types of cancer. Growing trends are also by other chemotherapy agents applied by nanotechnology, such as docetaxel, gemcitabine and cisplatin. Instead, since 2007 there is the development of new molecular target therapy, a new technological paradigm to treat the cancer based on small molecule and protein drugs, that has generating a revolution in clinical practice (Coccia, 2012b). Figure 3 shows growing trends of the association between target/antiestrogen therapy and nanotechnology are by cetuximab and tamoxifen. Cetuximab is a monoclonal antibody[9] that is approved to treat some patients with squamous cell carcinoma of the head and neck or colorectal cancer. Tamoxifen is a type of antiestrogen, a drug

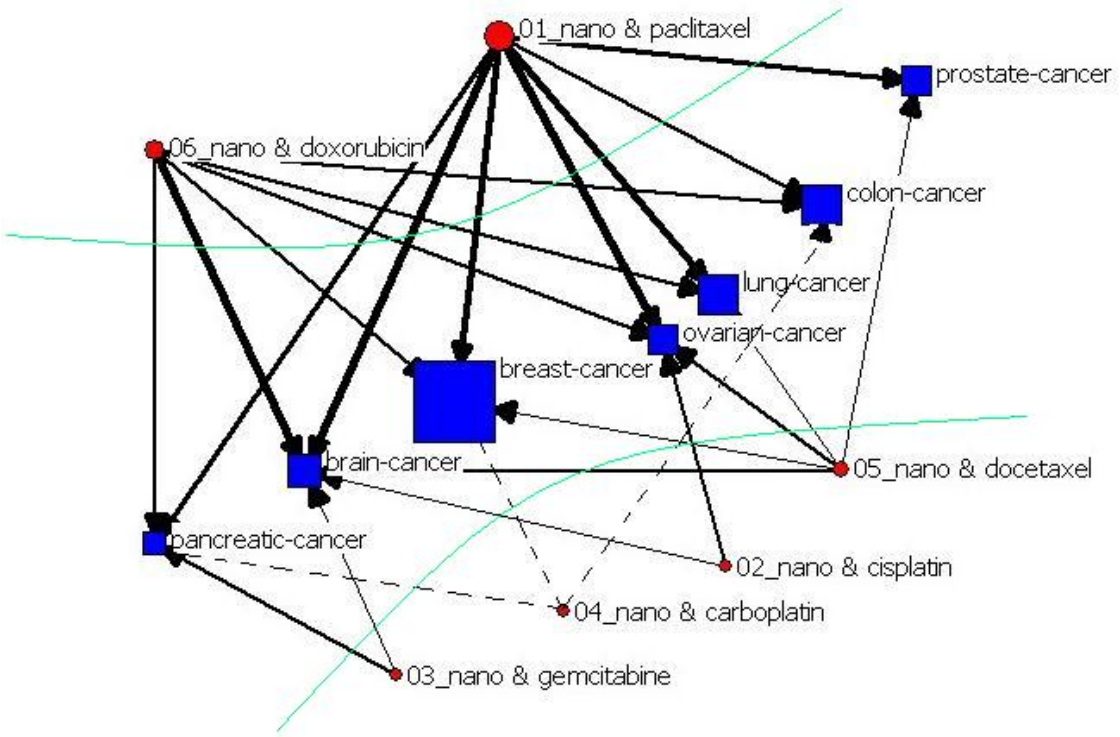
[9]"A type of protein made in the laboratory that can bind to substances in the body, including cancer cells. There are many kinds of monoclonal antibodies. A monoclonal antibody is made so that it binds to only one substance. Monoclonal antibodies are being used to treat some types of cancer. They can be used alone or to carry drugs, toxins, or radioactive substances directly to cancer cells" (National Cancer Institute, 2013).

used to treat certain types of breast cancer and to prevent breast cancer.

It blocks the effects of the hormone estrogen in the breast. Tamoxifen is also being studied in the treatment of other types of cancer. Herceptin (Trastuzumab) is one of the first target therapies applied by nanotechnology to cancer treatments; in particular, it is approved to treat certain types of breast cancer as well as some types of gastric or gastroesophageal junction adenocarcinoma.

Herceptin and nanotechnology trend achieved a peak in 2009, though now there is a declining trend of the technological trajectory. The trend of curcumin treatment by nanotechnology is growing. This substance has a current high interest in chemoprevention, in particular for serious gastrointestinal diseases such as colonrectum cancer (*cf.* Hull and Logan, 2011 and other articles in the issue of *Best Practice & Research Clinical Gastroenterology*, vol. 24 and 25). In short, Figure 3 shows two main technological waves concerning the application of anticancer treatments by nanotechnology:

1. The early technological wave is in the early 2000s and based on some types of chemotherapy agents with a broad spectrum of applications to different cancers;
2. The second technological wave appeared after 2006, with new nano-technological applications in both chemotherapy agents and molecular target therapy (*e.g.* lapatinib for breast and other solid tumors and cetuximab for head, neck and colorectal cancer).



Source: Authors' own calculation.

Figure 4: Network of main nanotechnology-based chemotherapy agents applied in different types of cancer.

Figure 4 and 5 show, by a network analysis, the field of action of chemotherapy agents or molecular target therapy that use nanotechnology to treat cancer.

In particular, Figure 4 shows that there are two clusters based on the association of chemotherapy agents and nanotechnology: *general* (No. 01 & 06) and *specific ones* (No.02, 03, 04 & 05).

The first cluster is doxorubicin and paclitaxel applied by nanotechnology (*see* the high number and larger thickness of arrows): these chemotherapy agents have a broad-spectrum of action (based on high number of citations) on different types of cancers. As a matter of fact, doxorubicin has a strong connection with brain cancer, whereas paclitaxel has a strong association meanly with brain, ovarian, breast and lung cancer.

The second cluster is given by other nanotechnology-based chemotherapy agents, which have a reduced spectrum of applications, more focused on specific cancers, such as: gemcitabine for pancreatic and brain cancer (the nanotechnology based gemcitabine agents also plays a main role to treat metastases of brain cancer), cisplatin for ovarian cancer, docetaxel for brain and ovarian cancer.

Figure 4 also shows that breast and lung cancer have a large volume of research records in this field concerning new treatments with nanotechnology (larger square), whereas nanotechnology associated to doxorubicin and paclitaxel is those more frequently cited.

Figure 5, instead, shows similar results for nanotechnology based on molecular target therapies and other anticancer substances (considering the number and thickness of arrows). Similarly to the previous results, Figure 5 presents also two groups of anticancer treatments based on nanotechnology, *i.e*. widely applied general molecular target therapy/substance with nanotechnology and specifically applied one. The curcumin substance for chemoprevention and cancer siRNA therapy applied by nanotechnology have a broad spectrum of applications on several types of cancer (curcumin has a strong connection mainly with brain, colon and prostate cancer-based on high citations-; siRNA with pancreatic cancer; *cf.* Yang *et al.*, 2012).

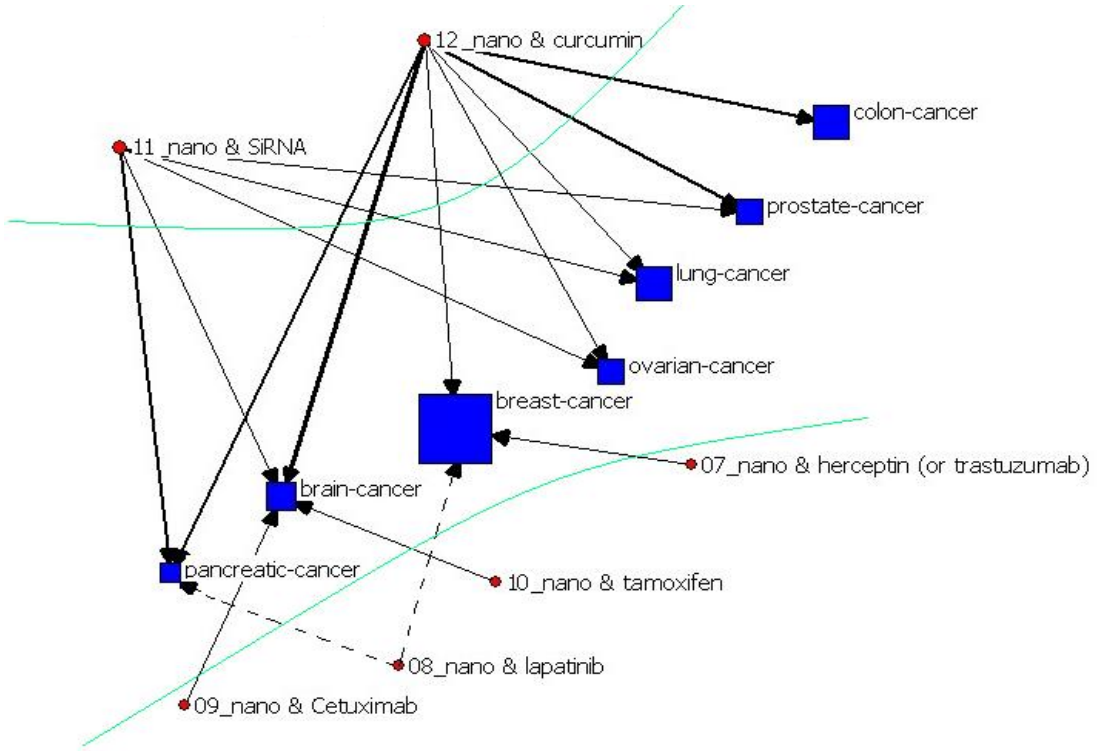
Herceptin *via* nanotechnology is applied mainly on breast cancer, cetuximab on brain cancer and lapatinib[10] for breast and pancreatic cancer. Figure 5 also shows an interesting connection between tamoxifen *via* nanotechnology and brain cancer.

Tamoxifen is most often used to treat or prevent breast cancer, however it has also been tried for other cancers, including brain tumors, however tamoxifen trial to treat brain cancer show that the effectiveness of this anticancer treatment has high uncertainty. As well as, an interesting connection is between lapatinib *via* nanotechnology and pancreatic cancer. In fact, based on in vitro results, lapatinib may provide clinical benefit in EGFR[11] positive pancreatic ductal adenocarcinoma (Walsh *et al.*, 2013).

As far as nanotechnology-based on molecular target therapy is concerned, breast, brain, lung and colon cancer have a larger volume of research records in these fields (larger square).

[10] Lapatinib is approved for the treatment of certain types of advanced or metastatic breast cancer.

[11] Epidermal growth factor receptor, *cf.* Coccia (2012b).



Source: Authors' own calculation.

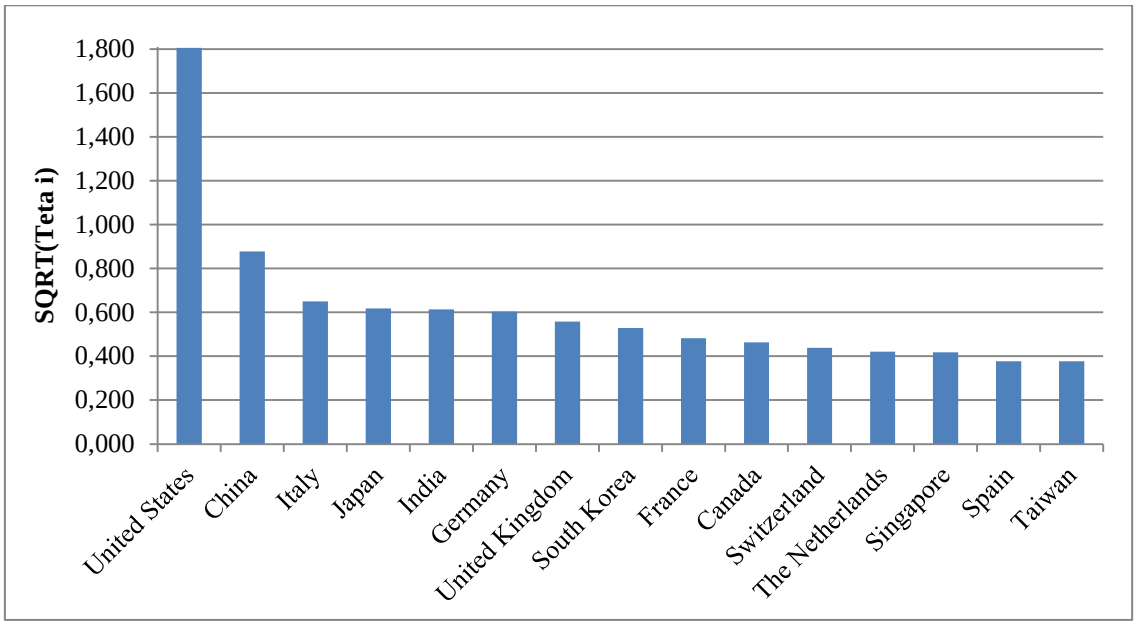
Figure 5: Network of main molecular target therapies applied by nanotechnologies for ground-breaking treatments in different types of cancers.

To explore the sources of the scientific research on ground-breaking applications of anticancer drugs *via* nanotechnology, we spot the top 15 performer countries in Figure 6. These high performer countries are mainly (in decreasing order with standardized value): USA, China, Italy, Japan, India, Germany and UK. These are also the countries with a high intensity of scientific research of anticancer drugs by nanotechnology in all specific types of cancer. However, Motoyama and Eisler (2013) argue that when academic publications are divided by number of researcher, the US is not the leader but lags behind the Germany and the United Kingdom.

Figure 6 makes a total comparison across countries, whereas Figure 7 shows the inner specialization of the countries in new anticancer drug applications by nanotechnology in specific type of cancer.

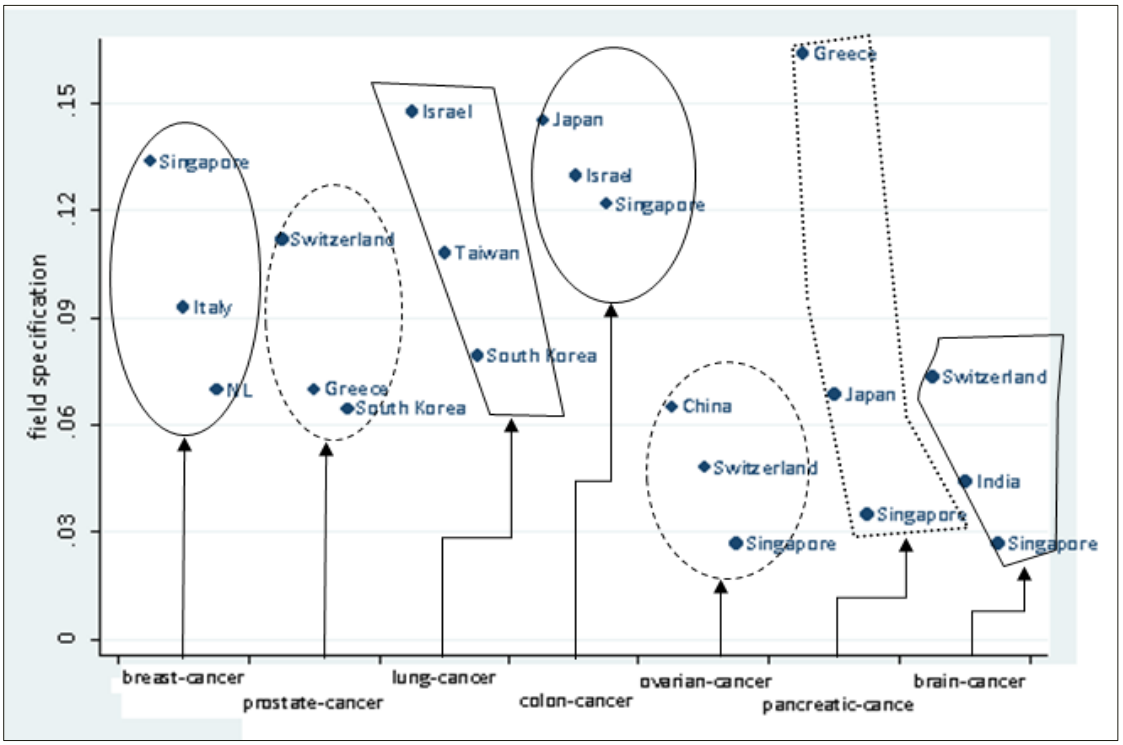
Field specialization index γ_{ij} (Eq. 4) indicates the specialization ratio of the country *i* in the specific research field *j*.

For instance, Singapore and Italy have a higher inner specialization in breast cancer (treated by nanotechnology-based anticancer drugs) in comparison to other types of cancer, Switzerland and Greece in prostate cancer, Israel and Taiwan in lung cancer, Japan and Israel in colon cancer, China and Switzerland in ovarian cancer, Greece and Japan in pancreatic cancer and for brain cancer, high inner specialization is within Switzerland and India. Detailed values for all countries and cancer research fields can be found in Table 1A in the Appendix.



Source: Authors' own calculation.
Note: Square root is applied to better represent the values.

Figure 6: Top 15 high performer countries in nanotechnology applied for cancer treatments (2000-2012)



Note: See detailed calculation equations in Section Method of Research.
Source: Authors' own calculation.

Figure 7: Inner specialization of countries (with high value γ) in nanotechnology applications to treat specific cancer

5. LESSONS LEARNED AND CONCLUDING OBSERVATIONS

Chemotherapy has non-specific effects in the body on normal tissues, causes toxicity, reduces the quality of life of patients, weakens the immune system and can damage in irreversible way the recovery power of patients. Instead, according to Gao *et al.* (2013): "nanotechnology-based chemotherapies seem to have an ability to specifically and safely reach tumor foci with enhanced efficacy and low toxicity". In particular, nanotechnology tends to support the discovery and clinical development of novel therapies for oncology focused on chemotherapy agents, small molecule and protein drugs (target therapy). Nanotechnology is contributing to create differentiated products and enhance clinical practice for new anticancer treatments (*cf.* Bertrand *et al.,* 2013). This groundbreaking pattern of nanotechnology in medicine is enhanced by mechanism of " 'learning via diffusion' …. The increased adoption of a technology paves the way for improvement in its characteristics" (Sahal as quoted by Coccia, 2014). The present paper analyses the new trajectories of ground breaking cancer treatments based on nanotechnology. Using publication and citation data, covering seven cancer fields and several types of anticancer treatments *via* nanotechnologies, our study shows here that some emerging directions of nanoscience and nanotechnology in oncology are growing rapidly over time.

Some main findings of this study are:

- *Technological waves.* The first main finding, over the studied 13 years, is represented by two main technological waves concerning the application of anticancer treatments by nanotechnology (Fig. 3). The early technological wave is in the early 2000s and based on some types of chemotherapy agents with a broad spectrum of applications to different cancers (e.g. doxorubicin and paclitaxel), while after 2006, the second technological wave appeared with narrow applications of molecular target therapy by nanotechnology (such as cetuximab, lapatinib, etc.). These nanotechnology waves in medicine are opening new and effective treatments for breast, lung, brain and colon cancers.
- *High rate of mortality as driver.* The second main finding is the recognition that, since the late 2000s, the sharp increase of several technological trajectories of nanotechnology-based anticancer drugs seems to be driven by high rates of mortality of some types of cancers (*e.g.* pancreatic and brain) in order to find more effectiveness therapies that increase the survival of patients. Hence, most importantly, nanotechnology opens a new era for anti-cancer treatments where mortality of some types of cancer is high and traditional drugs /approaches are not effective enough. In fact, in brain cancer and pancreatic-cancer (where mortality rate is high in comparison to the incidence, *see* Tab. 1), although the total research output is low, nanotechnology-based anticancer treatments seem to play an increasingly important role to find ground-breaking therapies that have high effectiveness and low adverse effects.
- *General and specific nanotechnology-based chemotherapy.* The third result is given by network analysis, which seems to show that there are both general and

specific nanotechnology-based chemotherapy: *the first one* is based on doxorubicin and paclitaxel applied by nanotechnology mainly to treat brain, ovarian, breast and lung cancer; *the second one* is based on gemcitabine for pancreatic and brain cancer, cisplatin for ovarian cancer, docetaxel for brain and ovarian cancer.

- *Likely new directions of path-breaking nanotechnology-based molecular cancer therapy*. These new directions, detected by network analysis, seem to be tamoxifen *via* nanotechnology to treat brain cancer and lapatinib *via* nanotechnology to treat pancreatic cancer.
- *Specialization of countries.* Another result is that some countries show an inner specialization in nanotechnology-based treatments for specific type of cancer, such as Singapore and Italy for breast cancer, Switzerland and Greece for prostate cancer, Israel and Taiwan for lung cancer, Japan and Israel for colon cancer, China[12] and Switzerland for ovarian cancer, Greece and Japan for pancreatic cancer and Switzerland and India for brain cancer.

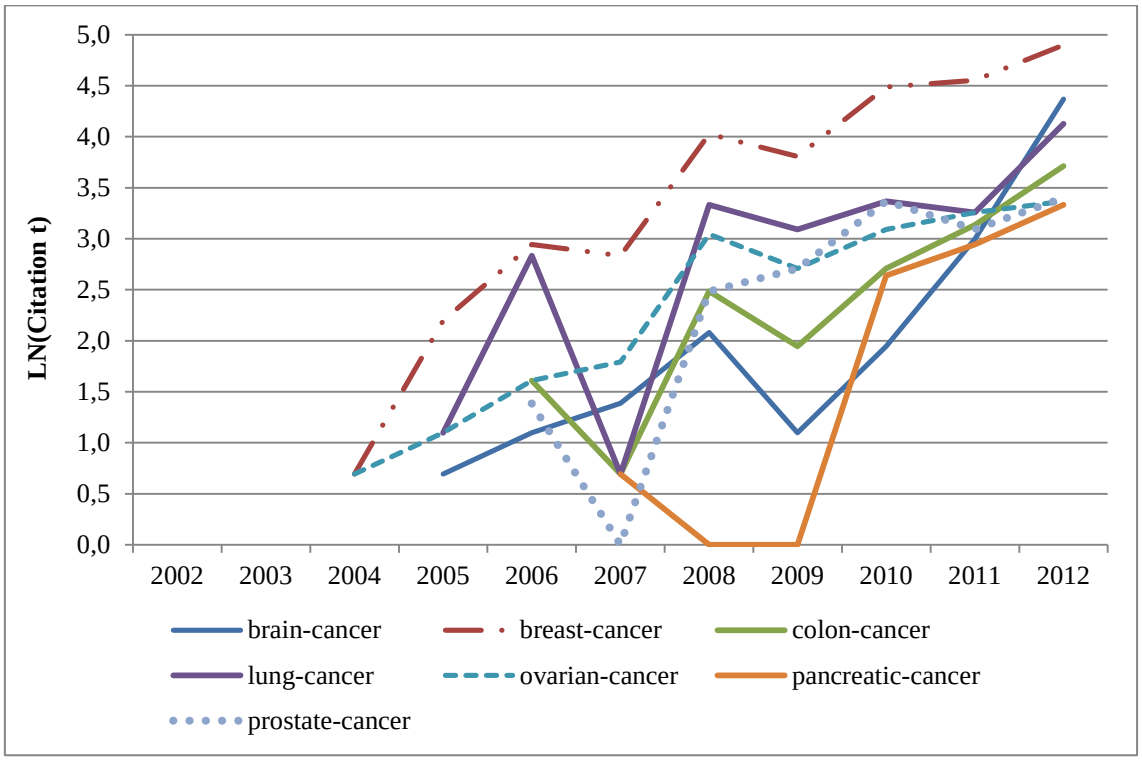
These results show vital patterns of nanoscience and nanotechnology in oncology. The technological trajectories detected may be the foundation for a continuous progress of nanotechnology in biomedicine, supported by a high intensity of scientific and technological production growth that accumulates technical knowledge and spurs ground-breaking and efficient anticancer treatments.

Hence, new nano-technological avenues are paving a pervasive diffusion in biomedical sciences and generating a revolution in clinical practice to treat (and we hope to cure) cancers in order to lead to longer, better and healthier living of societies in a not-too-distant future (Mangematin and Walsh, 2012).

However, emerging trajectories of nanoscience and nanotechnology are also problematic in medicine because have several and unpredictable directions, in particular when we know that in the life science systems other things are often not equal and can change in the presence of turbulent and fast-running technological change.

[12] *cf.* Motoyama *et al.* (2014).

APPENDIX



Note: The logarithm of publications is taken to better present the values.
Source: Authors' own calculation.

Figure 1A: Citations of nanotechnology in cancer treatments per different typology of cancer (2000-2012)

Table 1A: Specialization of countries in specific cancer based on new applications of anticancer drugs via ground-breaking nanotechnology (2000-2012)

COUNTRY	breast-cancer	prostate-cancer	lung-cancer	colon-cancer	ovarian-cancer	pancreatic-cancer	brain-cancer
Australia	-0.174	-0.050	-0.057	0.046	-0.022	-0.035	-0.026
Canada	-0.021	0.024	-0.016	-0.030	0.040	-0.010	-0.001
China	-0.003	-0.041	0.038	0.011	**0.065**	0.014	-0.023
France	0.045	-0.005	-0.028	-0.006	-0.060	0.012	-0.014
Germany	0.028	0.019	-0.018	-0.019	-0.023	-0.012	0.023
Greece	-0.113	**0.070**	-0.055	-0.011	-0.022	**0.164**	-0.042
India	-0.028	-0.053	0.025	-0.029	-0.058	0.027	**0.044**
Iran	-0.064	-0.017	0.072	0.042	0.012	0.016	-0.031
Israel	-0.069	0.035	**0.148**	**0.125**	-0.060	-0.002	-0.042
Italy	**0.093**	0.003	0.000	-0.006	-0.030	0.009	0.015
Japan	-0.004	-0.028	0.025	**0.145**	-0.002	**0.069**	0.016
Netherlands	**0.070**	-0.029	-0.091	-0.025	-0.062	0.030	-0.028
Singapore	**0.134**	-0.110	0.028	**0.122**	0.027	**0.035**	**0.027**
South Korea	0.050	**0.065**	**0.079**	0.048	0.006	-0.017	0.006
Spain	-0.002	-0.065	-0.104	0.017	-0.064	0.006	0.003
Sweden	-0.073	0.060	-0.042	0.035	**0.043**	-0.033	-0.042
Switzerland	-0.027	**0.112**	0.042	0.112	**0.048**	-0.033	**0.073**
Taiwan	-0.072	-0.065	**0.108**	0.106	-0.021	-0.036	-0.035
United Kingdom	-0.008	-0.040	-0.025	0.024	-0.029	-0.015	-0.007
United States	-0.012	0.032	0.007	-0.009	0.020	0.013	0.004

Note: if *i* is the country and *j* is the research field (*e.g.* Breast cancer), the location of the countries in the map is given by the index γ that indicates the high specialization of the country *i* in the specific research field *j*

$$C_{ij} = \frac{Pubblications_{\ ij}}{Total\ Publications_{\ i}};\ W_j = \frac{Total\ Pubblications\ j}{Publications\ Worldwide};$$

$$\gamma_{ij} = C_{ij} - W_j; \qquad j = 1, \dots, n.$$

In **Bold** the countries with the highest value γ; moreover, if the index γ>0 means high specialization in the scientific research in this type of cancer, whereas if γ < 0 means that there is lower specialization. High values γ means a higher intensive research activity in the specific cancer area.

Source: Authors' own calculation.

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