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

Mario Coccia [a,*], Lili Wang [b]

[a] CNR–National Research Council of Italy, Torino, Italy and RAND Corporation, Washington, USA
[b] UNU–MERIT, Maastricht, The Netherlands

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ABSTRACT

A fundamental question in the field of technological forecasting and foresight is how to detect likely fruitful technological trajectories in new research fields, such as nanomedicine. We confront this question by developing an approach based on trends and networks of vital variables, analyzed by bibliometrics, which endeavours to detect fruitful trajectories of nanotechnology applied to ground-breaking anti-cancer treatments. 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 of application, while after 2006 the second technological wave appeared with new applications of chemotherapy agents and molecular target therapy by nanotechnology. 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 anticancer drugs applied by nanotechnology seems to be driven by high rates of mortality of some types of cancers (e.g. pancreatic and brain) in order to find more effective anticancer therapies that increase the progression-free survival of patients: the so-called technological trajectories mortality driven. The study also points out that global research leaders tend to specialize in anticancer drugs, via nanotechnology, for specific cancers (e.g. Switzerland in prostate cancer, Japan in colon cancer, China in ovarian cancer 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 the not-too-distant future.


## 1. Introduction and the problem

Interdisciplinary theoretical and experimental results related to nanoscience and nanotechnology in the life sciences support the diagnosis, monitoring, prevention and treatment of diseases such as cancer, a leading cause of death in the western world (Fonseca et al., 2014). Traditional chemotherapy has low efficacy for some types of cancer and tends to generate severe adverse effects in healthy tissues (Coccia, 2014). The advent of nanotechnology in medicine is generating a vital technological change and a revolution in oncology and other fields (Islam and Miyazaki, 2010; Rafols and Meyer, 2010; Coccia, 2012b,c; Wolinsky et al., 2012; Madeira et al., 2013; Lim et al., 2010).[1] Bibliometrics is an important approach for investigating

* Corresponding author at: CNR–National Research Council of Italy, Via Real Collegio, n. 30, 10024 Moncalieri (Torino), Italy. Tel.: +39 011 68 24 925; fax: +39 011 68 24 966.
*E-mail address:* m.coccia@ceris.cnr.it (M. Coccia).

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

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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, generating new technological trajectories mainly in chemistry, medicine and engineering research fields (cf. Coccia, 2012b; Robinson et al., 2013). 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, 2011; Coccia, 2012a). Instead, Shapira and Wang (2010) show that some countries, such as the USA and China, are considered among the top nanotechnology research publishing countries. This result likely can be due to high R&D investments in vital research fields and incentives given to researchers to publish in Web of Science indexed journals (Lin and Zhang, 2007; Shapira and Wang, 2009 cf. Coccia, 2010; 2010a; 2014b; Coccia and Rolfo, 2007). However, Youtie et al. (2008) claim that publication counts do not necessarily equate to publication influence.

An interesting problem that deserves to be analysed in the field of the economics of innovation and technological foresight is how to detect the path-breaking directions of technological trajectories in oncology based on ground-breaking anticancer treatments. We confront this main issue by an approach based on trends and networks of critical variables pinpointed by bibliometrics in order to detect and analyse:

- new technological trajectories and directions of important anticancer treatments (chemotherapy agents, target therapies and chemopreventive substances) administered by new drug delivery systems based on nanotechnology;
- vital relationships between anticancer treatments based on new drug delivery systems that use nanotechnology and different cancers;
- countries that are best performers in applications of nanotechnology to treat cancers and their specialization to treat specific cancers with new drug delivery systems based on nanotechnology.

This study can provide important results concerning emerging and fruitful directions of ground-breaking anticancer treatments based on nanotechnology that may generate a revolution in clinical practice due to increased therapeutic efficacy and decreased toxicity of cytotoxic effects in healthy tissues.

## 2. Theoretical background and related works

Generally speaking, technological innovations involve "*the solution of problems*" (Dosi, 1988, p. 1125, original emphasis). The solution tends to be achieved by the technological paradigm, defined as a: "'model' and 'pattern' of solution of *selected* technological problems, based on *selected* principles derived from the natural science and on *selected* material technologies" (Dosi, 1982, p. 152, original emphasis; see also Nelson and Winter, 1982). In modern socio-economic systems, cancer is a main problem and remains a stressful condition and a leading cause of death worldwide (Fonseca et al., 2014, p. 626; Hull et al., 2014). "Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems" (US National Cancer Institute, 2014).

Science and technology are generating several patterns of technological innovation in order to find a solution to this problem for human population (Coccia, 2009, 2012d, 2013). Traditional treatments are based on chemotherapy agents that are not effective to treat and cure some types of cancer such as lung, pancreatic and ovarian cancer (Coccia, 2012a,b,c). In particular, according to Fonseca et al. (2014) actual treatments of cancer often offer limited efficacy with several secondary adverse effects as a result of severe cytotoxic effects in healthy tissues.

In general, technological paradigms are underpinned in advances of fundamental sciences, such as molecular biology, chemistry and so on. This basic scientific knowledge has to transit in applied sciences (such as engineering)[2] in order to be embodied in radical technological innovations that can generate fruitful solution to several socio-economic problems. Moreover, the technological progress is affected by *focusing devices* considered: "typical problems, opportunities, and targets that tend to focus the search process in particular directions" (Rosenberg as quoted by Dosi, 1988, p. 1127). These selective and finalized directions of innovative activities engender fruitful technological trajectories, which spur: "the activity of technological progress along the economic and technological trade-offs defined by a paradigm" (Dosi, 1988, p. 1128; cf. Sahal, 1981). Nelson (2008) seeks to clarify why certain technological paradigms support fruitful scientific and technological progress in comparison to others. Determinants include the economic and human resources,[3] aimed at strategic research and technology programmes, and to a lesser degree "effective demand" of markets (Nelson, 2008, p. 487; cf. Rosenberg, 1983). In addition, a main driver of technological trajectories is the "interest and goals" of professional "knowledge-seekers" (Clark, 1987, p. 40, original emphasis).

A main technological paradigm is the molecular biology and Linstone (2004, p. 192) stresses the importance of the molecular technology, which: "is defined by the focus on the molecular scale, with nanotechnology, biotechnology and materials science coming to the fore". The current "molecular technology era" (Linstone, 2004) is driving, more and more, new technological trajectories of path-breaking anticancer treatments. In fact, breakthroughs in nanotechnology are providing "a new dimension" to medicine by therapies integrated in nanoparticles, which are spurring new insights to ground-breaking cancer treatments (da Rocha et al., 2014). The National Cancer Institute's nanotechnology strategy started in 2004 to support multidisciplinary researchers in the applications of nanotechnology to anticancer treatments based on new drug delivery systems (Hull et al., 2014). As a matter of fact, the advent of nanotechnology is a great promise to revolutionize many fields such as oncology by advanced cancer treatments of drug delivery.[4] Correspondingly, R&D investments in biomedicine and nanomedicine have experienced an exponential growth since the early 2000s, such that: "cancer nanotherapeutics are

[2] Engineering can be considered an *intermediate scientific field* because it links basic sciences (such as physics) to practical technological applications in order to solve problems of different fields (cf. Nelson, 2008, p. 491 and p. 494).

[3] For instance, R&D intensity of countries, number of researchers in science and technology, etc. (cf. Coccia, 2008, 2011, 2012e).

[4] In this regard, several nanocarriers seem to overrule previous technologies, demonstrating increased therapeutic efficacy associated to decreased toxicity (Fonseca et al., 2014, p. 626*ff*).

progressing at a steady rate" (Bertrand et al., 2014). Moreover, pharmaceutical companies have formed strategic alliances and partnerships with biotechnology firms to improve and accelerate the drug discovery process of path-breaking anticancer treatments (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 in new emerging fields. Bibliometrics plays a main role to detect and map this continuous evolution (Wang, 2014), being associated with powerful software to analyse 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 technique in the study of new scientific knowledge.

Thomas et al. (2011) discuss nanoparticle ontology for cancer nanotechnology research to represent knowledge underlying nanomaterials involved in cancer research. Mogoutov and Kahane (2007) 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), and lexical queries. Zitt et al. (2011) argue that keywords act as main signals of scientific inquiry, while citations are more effective in identifying research streams. Zitt and Bassecoulard (2006) also apply 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, citations and network analysis to provide fruitful results to understanding this vital research field. Using a keyword mining approach, Wang et al. (2013) find that the general trend of integration in the application of nanotechnology fields is converging. Instead, the study by Arora et al. (2013) employs structured text-mining software to profile keyword terms and identify new nanotechnology-related keywords. This research strategy shows the main role of several emerging cited-subject categories of nanotechnology, particularly in the biomedical sciences.

In fact, 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., 2014). Coccia (2012b) displays that the current convergence of genetics, genomics and nanotechnology is the scientific backbones of new technological paradigms and trajectories in biomedicine and nanomedicine. This convergence of vital scientific fields (e.g. genetics, genomics, proteomics, etc.) is supporting innovative anticancer treatments and a revolution in oncology (Coccia, 2012b; 2014). There are several nanotechnologies applied in biomedicine for supporting anticancer treatments (Chen et al., 2011; He et al., 2010; Luo et al., 2011) such as nanoparticle, quantum dots, and carbon nanotube (see Appendix A for a brief description of some nanotechnologies in medicine). Some edge areas of bio-nanomedical applications (closer to molecular biology) are still at the stage of first experimental trials, such as the combination between nanoparticle and siRNA.[5]

Gao et al. (2014) show that nanomedicine, based on a targeted drug delivery system, significantly improves efficacy of 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, 2012d, 2013, 2014). Ferlay et al. (2013) show high mortality (based on Age-Standardized Rate[6]), 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).

In general, cancers 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 tumour growth and progression" (US National cancer institute as quoted by Coccia, 2012c, p. 276);
c) Anti-oestrogen therapy, such as tamoxifen, that blocks the effects of the hormone oestrogen in the breast;
d) Cancer siRNA therapy (siRNA seems to substantially better than antibodies, because it 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.

Considering this background, we confront the initial problem of the paper by detecting and analysing the fruitful directions of the trajectories of new anticancer treatments integrated in nanotechnology drug delivery systems considering different types of cancers. Next section describes study design and analysis framework of this paper.

## 3. Study design and method

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

- Nanotechnology-based chemotherapy drugs (cytotoxic anti-neoplastic drugs) such as Paclitaxel, Cisplatin, Gemcitabine, Carboplatin, Docetaxel, Doxorubicin, etc.;
- Molecular cancer therapies with nanotechnology delivery systems such as herceptin, cetuximab, lapatinib, tamoxifen (anti-oestrogen), and cancer siRNA therapy;

[5] 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.

[6] *Mortality*: Population weighted average of the area-specific country rates applied to the 2008 area population. *Age-standardized rate* (*W*): A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardized 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.

- Chemoprevention substances with nanotechnology delivery systems 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 year 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, and we focus on 12 important journal categories.[7] In total, this study covers 5080 publications (nano & cancer treatments), including 1440 cited references from nanotechnology. VantagePoint and Ucinet software are used for accurate and deeper analysis as well as for visualizing technological networks. The networks are also assessed by an *index of connectivity* $\gamma$ (between nanotechnology-based anticancer treatments and cancer fields) given by total number of edges (starting from nodes of advanced cancer treatments) divided by the number of nodes concerning cancer fields (cf. Cariola and Coccia, 2004, pp.164–166).

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.[8] In particular, No. 01–No. 06 are new anticancer treatments based on chemotherapy agents applied by nanotechnology, while target therapies applied with nanotechnology are Nos. 07, 08, and 09; anti-oestrogen 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),[9] 14) nano & HER2 (or HER-2), 15) nano & RNA, and 16) nano & PLGA (poly lactic glycolic acid)[10] also provide substantial information about ground-breaking applications of cancer treatments via nanotechnology. However, they do not represent anticancer drugs and 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 for some anticancer treatments is explored by citation analysis.
- *Step 3*: To link (within a *network*) nanotechnology and anticancer drugs with a specific cancer field.
  *Remark*: Some evolutionary trends are plotted and analyzed by a Log-Linear Regression models[11] that are estimated by Ordinary Least Squares Method to measure the acceleration of some technological trajectories. 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 ($\theta_i$) 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 specialization in treatments of specific cancers within 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 $\gamma_{ij}$.

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

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

[7] 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.

[8] Numbers 13, 14, 15 and 16 are not included in the figures in the 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.

[9] For EGFR and HER2, see previous footnote.

[10] 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 et al., 2012).

[11] The estimation of a linear relationship is based on the following model: $\mathrm{Log}Y_i = \alpha + \beta T_i + \varepsilon_i$; $i = 1,\ldots, n$ ($\varepsilon_i$ = Errors; T = Time). The method of Ordinary Least Squares provides the estimated coefficients of equations.

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

A high level of index $\gamma_{ij}$ indicates the high specialization of the country $i$ in the specific research field $j$.

In particular, $\gamma > 0$ means high specialization of the scientific research in this type of cancer, whereas if $\gamma < 0$ means that there is lower specialization. High values $\gamma$ means a higher intensive research activity in the specific cancer field 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 the trajectories of new anticancer treatments applied by nanotechnology is due to higher rate of mortality of some types of cancer.

In order to validate this HP, we apply nonparametric measures of association based on coefficients of correlation Tau-b of Kendall and of Spearman between average nanocitations and ratio mortality/incidence of cancer. The philosophy of research of this study considers the position that there can be no adequate knowledge where causes are unknown and analyses the phenomena to be explained by a scientific realism approach.

## 4. Experimental results

### 4.1. Temporal dimension

Fig. 1 shows that the number of scientific publications concerning cancer treatments integrated in nanotechnology is growing over time. 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, growth rate of scientific research by brain and pancreatic cancer is increased sharply in later years, although scientific production in early 2000 was low. Coefficient of regression (a proxy of growth over time) by brain and pancreatic cancer trends is higher than breast cancer. In addition, Fig. 1 shows a convergence of these trajectories in the long run. These results are confirmed by the citations of nanotechnology in these fields (see Fig. 1B in Appendix B).

Fig. 2 displays interesting findings concerning the trajectories of main anticancer treatments applied by nanotechnology. First of all, the scientific research of chemotherapy agents applied through nanotechnologies is started in 2002–2003 (see No.01–No.06), whereas the new molecular target therapies leveraged with nanotechnology are started later, 2007 or thereabouts (see No.07–No.12).

As a matter of fact, since 2002 the highest intensity of scientific research in new anticancer treatments is based on well-known chemotherapy agent paclitaxel (discovered in USA during 1960s) and doxorubicin (discovered in Italy over 1950s) with advanced delivery systems based on nanotechnology. The high growth of these anticancer drugs can be due to broad spectrum of applications to treat different cancers: 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 the anticancer drug paclitaxel contained in nanoparticles (very tiny particles of protein). This formulation seems to work better than other forms of paclitaxel and has fewer side effects. US 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.

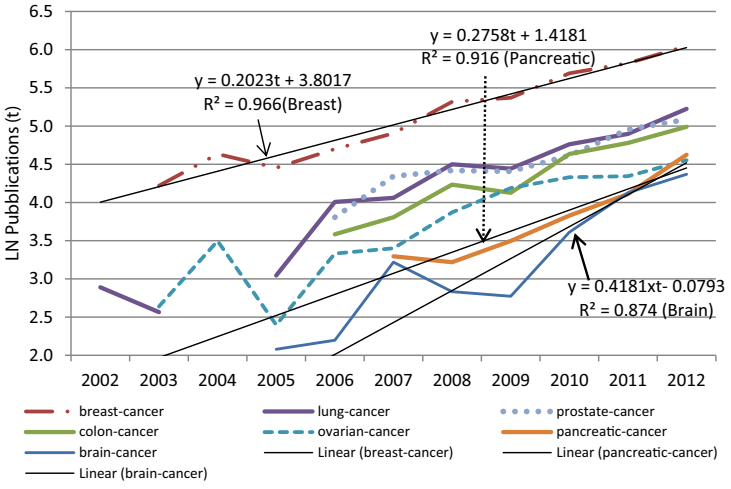


**Fig. 1.** Publications of cancer treatments integrated in nanotechnology for different typology of cancer (2000–2012). *Note*: the logarithm of publications is taken to better present the values. This figure also shows the estimate relationships by ordinary least square (and R square) to indicate approximate rate of growth of some trends.
*Source*: Authors' own calculation.

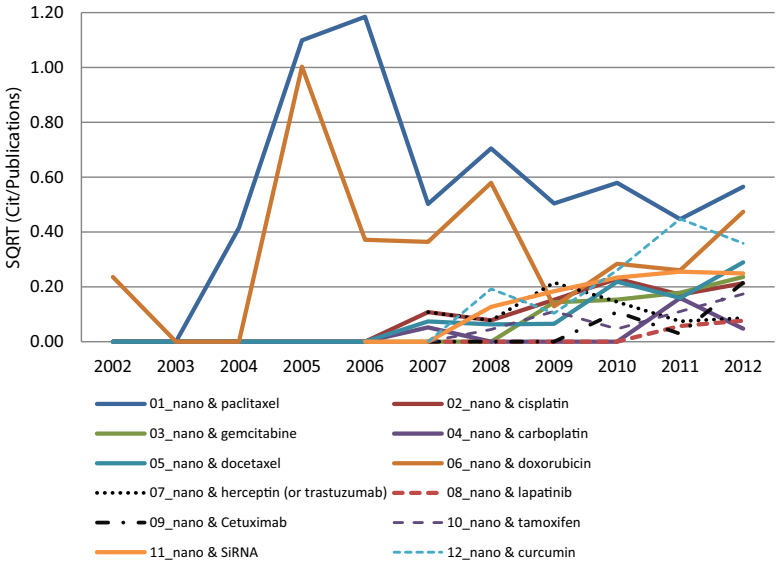


**Fig. 2.** Main nanotechnology streams associated to anticancer drugs (2000–2012). *Note*: 1) Chemotherapy agents applied with nanotechnologies are No. 01–No.06, while molecular target therapies and other anticancer treatments are No.07–No.12. 2) No.13–No.16 are not included in this figure because they do not concern anticancer drugs but EGFR, HER2, etc. 3) Square root (SQRT) is applied to better represent the values.
*Source*: Authors' own calculation.

- Pancreatic cancer that has metastasized. It is used with gemcitabine hydrochloride.

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 by small molecule and protein drugs, which is generating a revolution in clinical practice (Coccia, 2012c). Fig. 2 shows that growing trends of the association between target/anti-oestrogen therapy and nanotechnology are by cetuximab and tamoxifen. Cetuximab is a monoclonal antibody[12] that is approved to treat some patients with squamous cell carcinoma of the head and neck or colorectal cancer. Instead, tamoxifen is a drug used to treat certain types of breast cancer and to prevent breast cancer. In particular, it blocks the effects of the hormone oestrogen in the breast. Herceptin (trastuzumab) is one of the first target therapies applied by nanotechnology; it is approved to treat certain types of breast cancer as well as some types of gastric or gastroesophageal junction adenocarcinoma. Trend of herceptin by nanotechnology achieved a peak in 2009, though now this technological trajectory has a declining pathway. 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 colorectal cancer (cf. Hull and Logan, 2011 and other articles in vols. 24–25 of the journal *Best Practice & Research Clinical Gastroenterology*).

In short, Fig. 2 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 nanotechnology drug delivery systems for chemotherapy agents and molecular target therapies (e.g. lapatinib for breast and other solid tumours and cetuximab for head, neck and colorectal cancer).

### 4.2. Mortality-driven technological trajectories

To take the size of different research fields into account, we calculate the average of nano citation intensity concerning nano drug delivery systems 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 an average nano-citation intensity of 11.9%. Albeit the total research output of nanotechnology applications in breast cancer, colon cancer and prostate cancer is rather high (as showed in Fig. 1), the citation intensity of nanotechnology applied for ground-breaking anticancer treatments in these three cancer fields is relatively low (see the last three rows of the first column in Table 1).

[12] "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" (US National Cancer Institute, 2013).

In order to test the HP stated in section Study design and method, Table 1 shows the combination of factors of mortality and incidence rate of different cancer fields. It is interesting to observe that cancers in which the ratio of mortality to incidence (Called RaMI) is high, all have high nanocitation density, and vice versa. In fact, coefficients of correlation between average nanocitations and ratio RaMI are: Tau-b of Kendall = +0.59; Spearman = +0.76 (sig. 0.05). This result suggests that in cancer fields, where incidence is low while mortality is high, although the total joint research output of anticancer drugs with nanotechnology is relatively low, the intensity of nanotechnology applications to ground-breaking anticancer treatments is very high. Nanotechnology plays a crucial role in these specific cancers (with high mortality rate) because it might support new technological avenues with an increased therapeutic efficacy and decreased toxicity. These new technological trajectories can support effective therapies to increase the survival of patients. This result validates the HP and is confirmed by Fig. 3, where the high intensive citations of nanotechnology research are exactly in brain and pancreatic cancer. This statistical evidence seems in general to support the hypothesis that new directions of anticancer treatments integrated in nanotechnology can be explained by the high level of mortality of some types of cancers. These ground-breaking trends can be called technological trajectories mortality driven. This vital finding can underpin a main conceptual framework represented in the following scheme that runs from high-mortality cancer to path-breaking technological trajectories mortality driven (Fig. 4).

The main characteristic of these technological trajectories of new anticancer treatments mortality driven is to block the growth and spread of cancer. Some properties of these new technological trajectories are:

- *Fruitful therapeutic properties*:
  a) Enhancing therapeutic efficacy by induction of cancer cell cycle arrest (cf. Coccia, 2014a). The result of these advanced systems for cancer treatments is a better progression-free survival (PFS).[13]
  b) Reducing toxicity and side effect in healthy tissues by these nanotechnology-based anticancer treatments during PFS.
- *Innovative and scientific properties*:
  c) High mortality of some cancers induces innovations: the "necessity is the mother of invention" according to Ayres (1998, p. 289). In fact, high mortality cancers support higher R&D investments that spur an intensive scientific research by scholars and R&D teams. Stephan and Levin (1992) argue that scientists are interested in three types of rewards, 1) the satisfaction derived from solving a problem (a high mortality cancer is a main problem); 2) the recognition and the prestige that accompanies priority (e.g. a new discovery to treat and/or cure the cancer is a main recognition in scientific community); 3) the economic rewards that await after the success (e.g. patents of new drugs).
  d) Biology-driven anticancer medicine and new drug delivery systems based on nanotechnology (e.g. several nanocarriers) truly have the potential to address unmet medical needs in the field of oncology.
  e) "Learning via diffusion" (Sahal as quoted by Coccia, 2014a): the increased adoption of these new technological approaches of advanced anticancer drugs paves the way for improvements of its characteristics such as generation of new platforms of ground-breaking anticancer treatments based on nanoparticles.
  f) Multiplicity of learning mechanisms: bidirectional learning process from interaction between molecular biology and nanotechnology research.
  g) Higher scientific and technological rate of knowledge growth in comparison with traditional chemotherapy agents: high accumulation of knowledge in these fields to spur the development of ground-breaking anticancer treatments.
- *Economic properties*:
  h) These ground-breaking anticancer treatments tend to be cost effective and acceptable from a healthcare perspective in the long run rather than in the short run (Coccia, 2014).

**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 of cancer |
|---|---|---|
| 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 nanocitations 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.

### 4.3. Technological domains

In order to have a deeper understanding of the linkages between specific nanotechnologies and cancer fields, we use network analysis to illustrate the citation connections between nanotechnology and new treatments for different cancer fields. Our study explores how intensively each of the studied nanotechnology has been cited in cancer fields. In Section 4.1 we find that the growth rate of scientific research by brain and pancreatic cancer is increasing sharply in later years. Following

[13] Progression-Free survival: The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works (US National Cancer Institute, 2014).

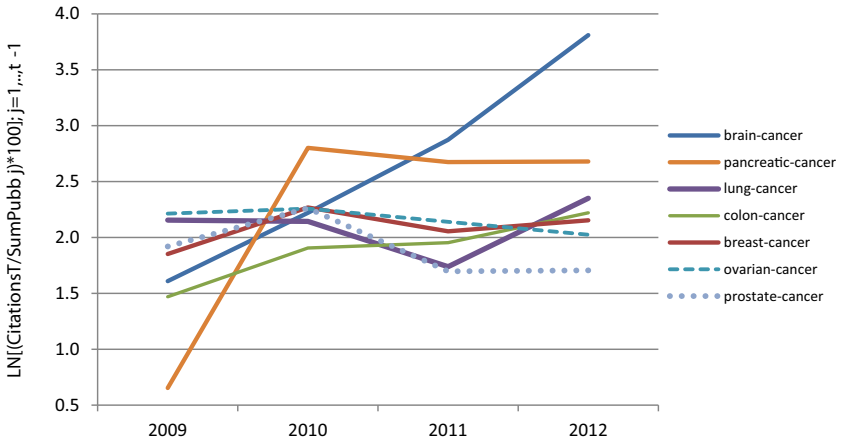


**Fig. 3.** Citation intensity of nanotechnology in cancer fields per different typology of cancer (2009–2012). *Note*: the logarithm of publications is taken to better present the values.
*Source*: Authors' own calculation.

that, we use network analysis to extract connections between specific cancers and advanced anticancer treatments by nanotechnology that have been driving/supporting the growth of new platforms for different cancers.

In fact, network analysis, represented in Figs. 5 and 6, shows the field of action of chemotherapy agents or molecular target therapy that uses nanotechnology to treat cancer. In these two figures, *arrow* represents the citation direction; *square nodes* are cancer fields; *circle nodes* are anticancer treatments by nanotechnology; *node size* represents the volume of publication. *Dense arrows* around one square node indicate that many types of nanotechnologies have been applied in this cancer field (considering citations of nanotechnology in new treatments for different cancers), while *sparse arrows* around a square node indicate that few nanotechnologies have been applied in this field.

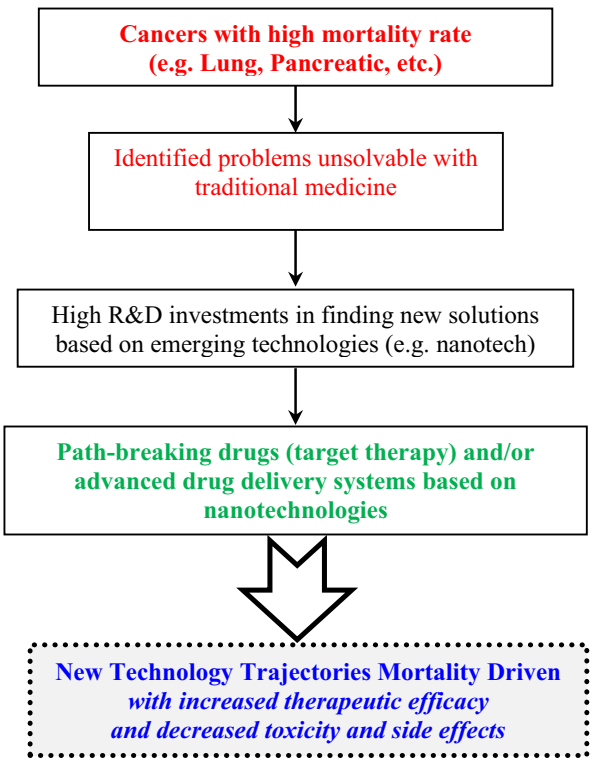


**Fig. 4.** Scheme of technological trajectories mortality driven.

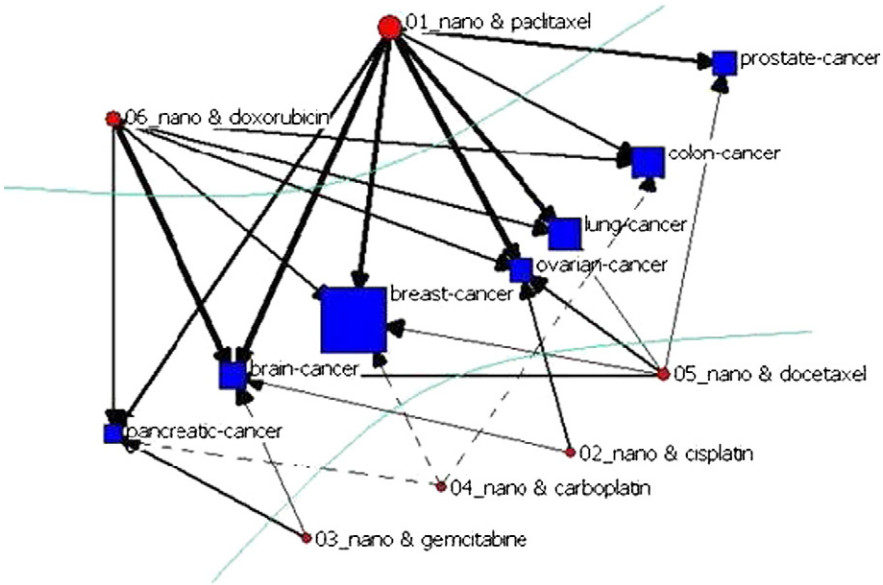


**Fig. 5.** Network of main nanotechnology-based chemotherapy agents applied in different types of cancer. *Note*: *arrow* represents the citation direction; *square nodes* are cancer fields; *circle nodes* are anticancer treatments by nanotechnology; *node size* represents the volume of publication.
*Source*: Authors' own calculation.

In particular, Fig. 5 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 play a main role to treat metastases of brain cancer), cisplatin for ovarian cancer, and docetaxel for brain and ovarian cancer. Fig. 5 also shows that breast and lung cancer have a large volume of research records in this field concerning new treatments with nanotechnology as drug delivery systems (larger square), whereas nanotechnology associated to doxorubicin and paclitaxel is more frequently cited.

Fig. 6, instead, shows similar results for nanotechnology-based molecular target therapies and other anticancer substances (considering the number and thickness of arrows). Similar to the previous results, Fig. 6 presents also two groups of new anticancer treatments based on nanotechnology, i.e. widely set of applied 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; importantly, targeted delivery of siRNA for gene silencing therapy has made its way to the clinic using lipid-polymeric-based particles, cf. Fonseca et al., 2014). Herceptin via nanotechnology is applied mainly on breast cancer, cetuximab on brain cancer and lapatinib[14] for breast and pancreatic cancer.

Fig. 6 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 tumours; however tamoxifen trial to treat brain cancer shows that the effectiveness has high uncertainty (Cancer Research UK, 2014). An interesting connection is between lapatinib via nanotechnology and pancreatic cancer. In fact, based on in vitro results, lapatinib may provide clinical benefit in pancreatic ductal adenocarcinoma (Walsh et al., 2013).

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

The *Index of connectivity* $\gamma_1$ between nanotechnology-based chemotherapy agents and cancer fields is equal to $\gamma_1 = 25$ /

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

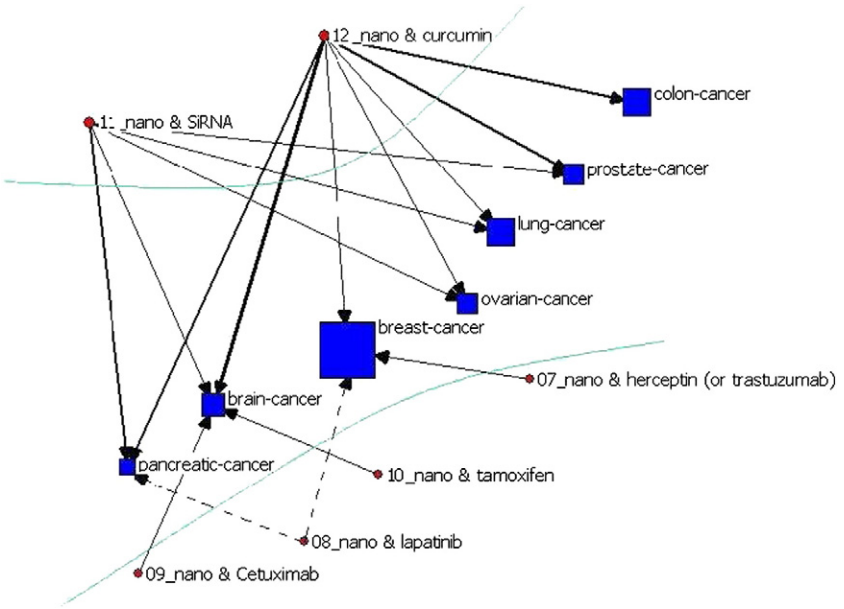


**Fig. 6.** Network of main molecular target therapies applied by nanotechnologies for ground-breaking treatments in different types of cancers. *Note*: *arrow* represents the citation direction; *square nodes* are cancer fields; *circle nodes* are anticancer treatments by nanotechnology; *node size* represents the volume of publication. *Source*: Authors' own calculation.

$7 = 3.57$, whereas $\gamma_2$ between nanotechnology-based target therapies/chemopreventive substances and cancer fields is equal to $\gamma_2 = 17 / 7 = 2.43$.

This result shows that the first network based on nanotechnology-based chemotherapy agents has a higher connectivity: higher applications of these advanced systems for treatments of different cancer, in comparison to nanotechnology-based target therapies/chemopreventive substances. This finding is also due to the new and rather unexplored research field of target therapies compared to chemotherapy as cancer treatments. This also supports the finding in Section 4.1 that molecular target therapies are in the second technological wave of diffusion and some applications are at the beginning of the technological development and at the frontier of scientific research in oncology.

### *4.4. Spatial concentration and specialization*

Following the analysis on the temporal trajectory and technological domains, it is of interest to understanding the spatial concentration, across countries, of the scientific research on ground-breaking applications of anticancer drugs via nanotechnology. Figs. 7 and 8 provide a main comparison of the top 15 performers at the national level.

These high performer countries are mainly (in decreasing order with standardized value): USA, China, Italy, Japan, India, Germany and UK (see Fig. 7). 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 (2011) argue that when academic publications are divided by the number of researchers, the USA is not the leader but lags behind Germany and the United Kingdom.

Fig. 7 makes a total comparison across countries, whereas Fig. 8 shows the inner specialization of the countries in new anticancer drug applications by nanotechnology in specific type of cancer.[15] Field specialization index $\gamma_{ij}$ (Eq. (4)) indicates the specialization ratio of the country *i* in the specific research field *j*. Fig. 8 shows that Singapore and Italy have a higher inner specialization in anticancer treatments of the breast cancer (treated by nanotechnology) 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 by Switzerland and India. Detailed values for all countries and cancer research fields are in Table 1B in Appendix B.

## 5. Discussion and concluding observations

Chemotherapy, as anticancer treatments, induces cytotoxic effects in healthy tissues, causes toxicity, reduces the quality of life of patients, weakens the immune system and can damage in irreversible way the recovery of patients. The nanotechnology is a great promise that is revolutionizing the oncology by new drug delivery systems, such as several nanocarriers (Fonseca et al., 2014). According to Gao et al. (2014): "nanotechnology-based chemotherapies seem to have an ability to specifically and safely reach tumour foci with enhanced efficacy and low toxicity". In particular,

[15] *See* Coccia, 2005, 2007 for some metrics of country performances.

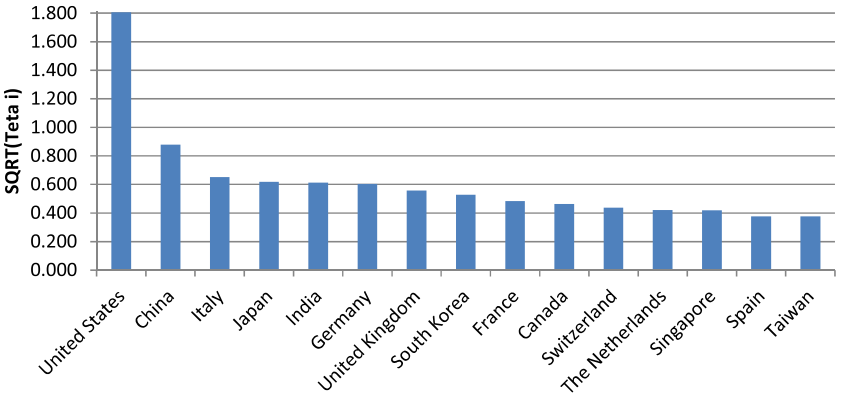


**Fig. 7.** Top 15 high performer countries in nanotechnology applied for cancer treatments (2000–2012). *Note*: square root (SQRT) is applied to better represent the values.
*Source*: Authors' own calculation.

nanotechnology tends to support the clinical development of advanced therapies in oncology by novel drug delivery systems for chemotherapy agents, small molecule and protein drugs (target therapy) and chemopreventive substances. Nanotechnology is contributing to create differentiated anti-cancer treatments for a fruitful personalized medicine that enhances the clinical practice (cf. Bertrand et al., 2014). This ground-breaking pattern of nanotechnology in medicine is improving by "'learning via diffusion' ….. The increased adoption of a technology paves the way for improvement in its characteristics" (Sahal as quoted by Coccia, 2014a).

The present study uses publication and citation data, covering seven cancer fields and several types of anticancer treatments via nanotechnologies, and shows some emerging directions of nanoscience and nanotechnology in oncology that are growing rapidly over time.

Some main findings of this study can be summarized as follows:

- Temporal dimension
  *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. 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

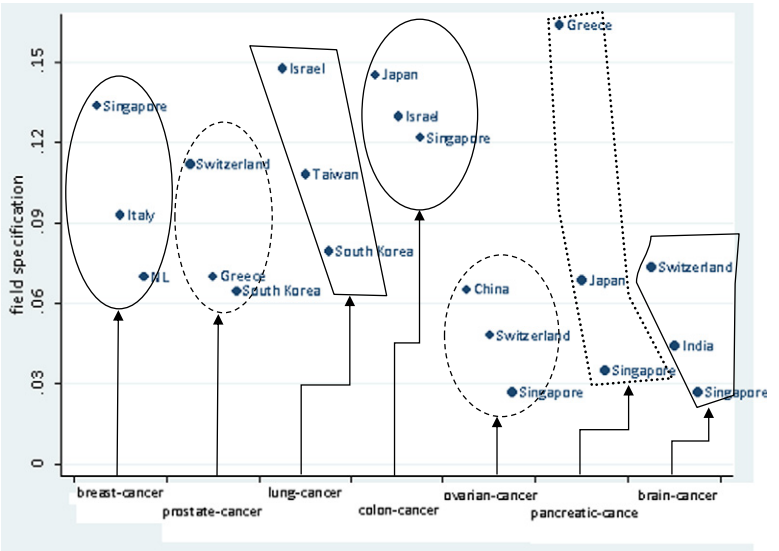


**Fig. 8.** Inner specialization of countries (with high value γ) in nanotechnology applications to treat specific cancer. *Note*: see detailed calculation equations in Section Study Design and Method.
*Source*: Authors' own calculation.

technological wave appeared with narrow applications of molecular target therapy by nanotechnology (such as cetuximab and lapatinib). These technological waves of drug delivery systems by nanotechnology in oncology are opening new and effective treatments for breast, lung, brain and colon cancers.

- Mortality (problem) driven
  *High rate of mortality of some cancers is a main driver of technological trajectories of advanced systems for cancer treatments*. 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, lung and brain) in order to find more effective therapies that increase the survival of patients and reduce toxicity of chemotherapy. Hence, most importantly, nanotechnology opens a new era for anticancer treatments where mortality of some types of cancer is high and traditional drugs/approaches are not effective enough. In fact, in brain cancer, lung cancer and pancreatic-cancer (where mortality rate is high in comparison to the incidence, see Table 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 (e.g. paclitaxel albumin-stabilized nanoparticle formulation).
- General and specific systems for cancer treatments
  The third result is given by network analysis, which seems to show that there are both general and specific nanotechnology-based chemotherapies: *the first set* is based on doxorubicin and paclitaxel applied by nanotechnology mainly to treat brain, ovarian, breast and lung cancer; *the second set* is based on gemcitabine for pancreatic and brain cancer, cisplatin for ovarian cancer, and docetaxel for brain and ovarian cancer. Similar results for nanotechnology-based target therapy. *Likely new directions of path-breaking nanotechnology-based molecular cancer therapy*, detected by network analysis, seem to be tamoxifen via nanotechnology to treat brain cancer and lapatinib via nanotechnology to treat pancreatic cancer.
- Spatial dimension: concentration and specialization of countries
  Another result is that some countries show an inner scientific specialization in nanotechnology based treatments for specific types 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[16] and Switzerland for ovarian cancer, Greece and Japan for pancreatic cancer and Switzerland and India for brain cancer.

These findings show vital patterns of nanoscience and nanotechnology in oncology. In fact, nanotechnology is opening new trajectories for anticancer treatments where the mortality of some types of cancer is high and traditional drugs/approaches are not efficient and generate high toxicity in healthy tissues (cf. Coccia, 2012a). 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 more and more ground-breaking and efficient anticancer treatments over time.

New nanotechnologies seem to be blazing a trail in biomedicine and generating a revolution in oncology, in order to lead to more effective anticancer treatments in the near future (cf. Coccia, 2012b; Mangematin and Walsh, 2012). Admittedly, considering the complex of emerging technologies and entangled medial fields, the definite long-run trend of the technological trajectories in advanced cancer treatments is yet unpredictable.

[16] Cf. Motoyama et al. (2014).

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This research started in 2012 by authors and further developed in 2013 while Mario Coccia was a visiting scholar at UNU–MERIT in Maastricht. We thank Prof. Bart Verspagen and Secondo Rolfo for the fruitful suggestions to this paper. Mario Coccia gratefully acknowledges the CNR–National Research Council of Italy for the financial support to this research project by the short mobility programme at UNU-MERIT (N. 0045595 of the 25 July 2013). Preliminary results have been presented at the S.NET 4th Annual Meeting of the society for the study of nanoscience and emerging technologies (22–25 October 2012), University of Twente (The Netherlands). The usual disclaimer applies.

## Appendix A

- Nanoparticles (NPs) can be designed to selectively target the specific tissue/organ in which there is the cancer (Coccia, 2012c). In addition, NPs with specific and appropriate ligands can be drug carriers to target selectively the tissue/organ affected by cancer (see Pöselt et al., 2012; Shukoor et al., 2012; Shukoor et al., 2011). Nanoparticles also act as carriers for drugs by organic nanomicelles or porous inorganic nanoparticles that, with apt bioactive systems, can target tumoral cells of the body (see Yao et al., 2011; Goel et al., 2010).
- Quantum Dots (QDs) are a specific subset of NPs and are mainly applied as targeted drug delivery (Obonyo et al., 2010; Byers and Hitchman, 2011; Rosenthal et al., 2011; 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).

**Appendix B**

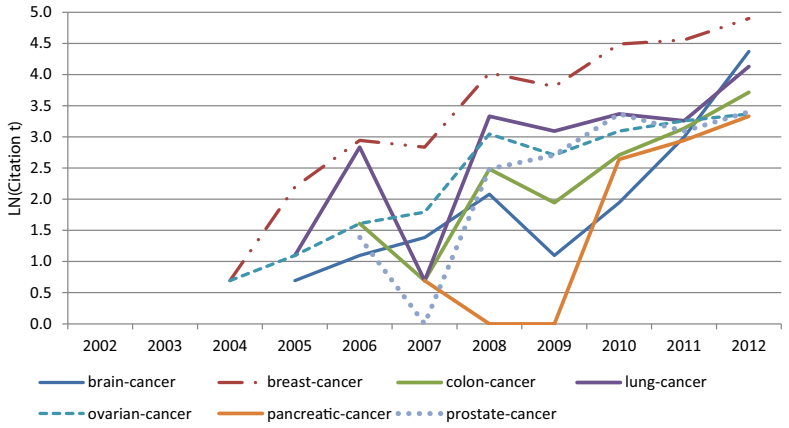


**Fig. 1B.** Citations of nanotechnology in cancer treatments per different typology of cancer (2000–2012). *Note*: the logarithm of publications is taken to better present the values.
*Source*: Authors' own calculation.

**Table 1B**
Specialization of countries in specific cancer based on new applications of anticancer drugs via ground-breaking nanotechnology (2000–2012).
*Source*: Authors' own calculation.

| 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 of Fig. 8 is given by the index $\gamma$ that indicates the high specialization of the country $i$ in the specific research field $j$

$$C_{ij} = \frac{Publications_{ij}}{Total\ Publications_{\ i}}; \quad W_j = \frac{Total\ Publications\ j}{Publications\ Worldwide}; \quad \gamma_{ij} = C_{ij} - W_j; \quad j = 1, \ldots, n.$$

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

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**Mario Coccia** is a researcher at the National Research Council of Italy and visiting professor of Industrial Organization and Economics of Innovation at the University of Piemonte Orientale (Italy). He has been a research fellow at the Max Planck Institute of Economics and visiting professor at the Polytechnics of Torino. He has conducted research work at the Georgia Institute of Technology, Yale University, UNU-Maastricht Economic and Social Research Institute on Innovation and Technology (United Nations University-MERIT), University of Maryland (College Park), Bureau d'Économie Théorique et Appliquée (University fo Strasbourg), Munk School of Global Affairs (University of Toronto), RAND Corporation (Washington) and Institute for Science and Technology Studies (University of Bielefeld). He has written extensively on Economics of Innovation and Management of Technology; his research publications include more than two hundred fifty papers in several disciplines.

**Lili Wang** obtained her PhD degree from Eindhoven University of Technology in 2009 and currently works at United Nations University–Maastricht Economic and Social Research Institute on Innovation and Technology (UNU–MERIT), The Netherlands. Her research focuses on technological changes, S&T economics, and analysis of emerging technologies (in particular nanotechnology). She has conducted various nanotechnology research projects and her work has been widely published in peer-reviewed journals.