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Analisi scientometrica dei campi scientifici e delle tecnologie emergenti nelle nano-bio-tecnologie che stanno generando una rivoluzione in medicina:
L'analisi delle terapie innovative per la cura dei tumori

Preliminary Version (DRAFT)

Scientometrics to detect the emerging nano-technological trajectories in cancer research

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ABSTRACT: The purpose of this paper is to analyze the trajectories of nanotechnologies applied to path-breaking cancer treatments to detect ground-breaking and fruitful directions in medicine. Results tend to show two main technological waves of nano applications in cancer treatments. The early wave was embodied in some types of chemotherapy agents with broad spectrum in early 2000, while after 2006, there appeared the second wave with new nano-technological applications in both chemotherapy agents and target therapy. Widely applications of nanotechnology have been detected in breast, lung, brain and colon cancers. In addition, since late 2000, the sharply increase of the several technological trajectories of nanotechnologies and anticancer agents seem to be driven by high rate of mortality of some types of cancers (e.g. pancreatic and brain) in order to find more effectiveness therapies. The study here also shows that worldwide leader countries in these research fields are USA, China, Italy and Japan, whereas some countries are more specialized in applications of nanotechnology in specific cancer such as prostate cancer (Switzerland), colon (Japan), ovarian (China) and pancreatic cancer (Greece). The directions of these ground-breaking technological trajectories are paving new pathways 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, Target Therapy, Chemotherapy, Biomedicine, Nanomedicine, Nanoparticles, Cancer, Bibliometrics, Publications.

JEL-CODES: C89; O30, C53, I10;

MATHEMATICS SUBJECT CLASSIFICATION (MSC2010): 91; 92

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Contents

1. Introduction and objective of the research

Nanotechnology is a current vital research field that is also supporting innovation and change in modern biomedicine and biomedical engineering (Islam and Miyazaki, 2010; Rafols and Meyer, 2007; Rafols and Meyer, 2010; Coccia, 2012a; Madeira *et al.*, 2013; Tierney *et al.*, 2013). In fact, nanotechnologies have a high potentiality of development for biomedical purposes such as the ground-breaking applications in new therapies to treat serious diseases (*cf.* Lim *et al.*, 2010; Coccia, 2012a). 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.* Bárcena *et al.*, 2009; Sylvester and Bowman, 2010; Coccia, 2012).

Bibliometrics is an important approach for investigating emerging fields of nanotechnology (Arora *et al.*, 2013). 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 (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 US and China, which are considered among the top nanotechnology research publishing countries. This result can be due to both high R&D investments in this vital research field and incentives given to researchers to publish in WoS indexed journals (Lin and Zhang, 2007; Shapira and Wang, 2009). However, Youtie *et al.* (2008) argue that publication counts do not necessary equate to publication influence.

The purpose of this paper is to analyze the new directions of trajectories that concern the vital applications of nanotechnologies in cancer treatments to detect path-breaking pathways. In particular, this study pinpoints:

- the technological trajectories of most common anticancer drugs (chemotherapy agents, substances, molecules 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 inner specialization of countries in new applications to treat specific cancer.

This study can provide main information concerning emerging directions of nanotechnology in cancer therapy that is generating a revolution in clinical practice to improve human health and quality of life in a not-too-distant future.

2. Theoretical background

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). Social scientists, more and more, use bibliometric and scientometric approaches to detect trajectories in the wide domain of nanotechnologies. In fact, with the widely application of nanotechnology in almost all research fields (Wang, et al. 2013), these approaches are of great importance to explore the current knowledge growth and trajectories in nanotechnology research that may support future patterns of technological innovation in emerging research fields, such as biomedicine. Data generated from cancer nanotechnology research are so diverse and large in volume, difficult to use without apt software. Thomas *et al.* (2011) present 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 identifies 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. De Bellis (2009) observes that citation analysis is a prominent feature in the study of scientific knowledge. For instance, Zitt and Bassecoulard (2006) employ citation networks to expand their corpus of nanotechnology publications. Instead, Leydesdorff and Zhou (2007) present an approach based on core set of six nanotechnology journals and citation, and network analysis to provide fruitful results in this research field.

Among all the research categories, 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; Sekhon and Kamboj, 2010; Sekhon and Kamboj, 2010b; Willner and Willner, 2010). Coccia (2012a) displays that the current convergence of genetics, genomics and nanotechnology is one of the scientific backbones of new technological paradigms that link several

technological trajectories in biomedical sciences. This convergence of new scientific fields supports innovative anticancer treatments that have been generating a revolution in clinical practice.

Kim *et al.* (2010, p. 2434) state:

> "Nanomaterials are now being designed to aid the transport of diagnostic or therapeutic agents through biologic barriers; to gain access to molecules; to mediate molecular interactions; and to detect molecular changes in a sensitive, high throughput manner. In contrast to atoms and macroscopic materials, nanomaterials have a high ratio of surface area to volume as well as tuneable optical, electronic, magnetic, and biologic properties, and they can be engineered to have different sizes, shapes, chemical compositions, surface chemical characteristics, and hollow or solid structures. These properties are being incorporated into new generations of drug-delivery vehicles, contrast agents, and diagnostic devices".

There are several nanotechnologies applied in biomedicine for cancer treatments (Chen *et al.*, 2011; He *et al.* 2010; Luo *et al.*, 2011). For instance, Nanoparticles (NPs) are nanoscopic spheres ranging in diameter up to some tenths of nanometers[1] that can be made of metals, metallic salts or oxides, or can have a biological origin. NPs can be designed to selectively target the specific tissue/organ in which there is the cancer (Wolinsky *et al*., 2012; Coccia, 2012b). Kumar and Mohammad (2011, p. 789ff) show the potential opportunities for the combination of magnetic nanoparticle-based hyperthermia therapy and controlled drug release paradigms towards successful applications in personalized medicine. 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 (Pöselt *et al.*, 2012; Shukoor *et al.*, 2012; Shukoor *et al.*, 2011). Nanoparticles and nanomicelles 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). Gold nanoparticles and Gold nanorods[2], due to their electronic structure, heat themselves when exposed to strong electromagnetic radiations, like those emitted by lasers (Ratto *et al.*, 2011; Ungureanu *et al.*, 2011). This biomedical procedure uses heat to kill cancer cells (El-Sayed *et al.*, 2006). Quantum Dots (QDs), instead, are a specific subset of NPs (Obonyo *et al.*, 2010; Byers and Hitchman, 2011; Rosenthal *et al.*, 2011). Interesting applications of QDs in medicine are as targeted drug delivery, photodynamic therapy, etc. (Jain, 2012; Chatterjee *et al.*, 2008; Azzazy *et al.*, 2007). In addition, the bioconjugation of the surface of QDs with biomolecules (e.g. antibodies, oligonucleotides, DNA, etc.) gives the property of targeting them onto specific locations in the body to kill tumor cells.

[1] A nanometer (nm) is equal to one millionth of millimeter.

[2] Nanorods are a specific morphology of nanoscaled objects. The main difference from nanoparticles is their elongated shape. Each of their dimensions range from 1 to 100 nm. They may be synthesized from metals or semiconducting materials.

Carbon nanotubes are an allotropic form of carbon, having cylindrical structure. A main feature is the possibility of being used to deliver drugs against cancers (Ezzati Nazhad Dolatabadi *et al.*, 2011; Bareket *et al.,* 2010). In fact, their tubular structure allows both carrying drugs and protecting them towards external agents. Therapeutic applications of carbon nanotubes combined with cytotoxic (antineoplastic or chemotherapy) agents are a key area of development for biomedical sciences (Shapira *et al.*, 2011). Immunotherapy is another new frontier for future therapeutic treatment of cancer based on nanotechnology. In particular, the combination of nanoparticles and lymphocytes, such as *T*-cells[3], may have new applications for effective cancer treatments (see Hamdy *et al.*, 2011; Hung *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 nanovector and siRNA or mi-RNA4.

These nanotechnologies have been widely applied in cancers that have high incidence and mortality. GLOBOCAN (2008) shows high mortality in terms of Age-standardized rate[5] 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). We focus on main applications of nanotechnologies to treat these types of cancers. In particular, we analyze the likely technological trajectories concerning current applications of anticancer drugs *via* nanotechnologies to detect future main directions in:

- Nanotechnology with chemotherapy agents such as Paclitaxel, Cisplatin, Gemcitabine, Carboplatin, Docetaxel, Doxorubicin, etc.;
- Nanotechnology with target therapies[6] such as herceptin, cetuximab, lapatinib, tamoxifen (hormone therapy), and molecules siRNa
- Nanotechnology with chemoprevention substances such as curcumin.

Next section describes a methodology to analyze these vital topics.

[3] T cells or T lymphocytes belong to a group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity. The abbreviation *T* stands for thymus, since this is the principal organ responsible for the T cell's maturation.

[4] Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA molecules, 20-25 nucleotides in length, that play a variety of roles in biology. MicroRNAs (miRNAs) are short ribonucleic acid (RNA) molecules, on average only 22 nucleotides long and are found in all eukaryotic cells, except fungi, algae, and marine plants.

[5] *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.

[6] Targeted cancer therapies are: " 'drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression" (Coccia, 2012b, p. 276)

3. Research design and methodology of research

This study focuses on the application of nanotechnology to treat some main typology of cancers. Considering the high mortality 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. The search query was developed by the combination of nano and each cancer field searched from abstract-keywords and title. The time span covers 13 years (2000-2012). To refine the data quality, we excluded publications appeared in less relevant journal sources, e.g. social science, etc., but focus on 12 important journal categories[7]. In total this study covers 5,080 (nano & cancer treatment) publications, including 1,440 cited references from nanotechnology. VantagePoint and Ucinet software are used for deeper analysis and visualization.

After gathering all the publication records, we classify the applications of nanotechnology into different groups by keyword. We focus on 16 vital types of nanotechnologies that are used with anticancer drugs. The 16 nanotechnology 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 & EGFR (or epidermal), 11) nano & HER2 (or HER-2), 12) nano & tamoxifen, 13) nano & siRNA, 14) nano & RNA, 15) nano & PLGA(poly lactic glycolic acid), 16) nano & curcumin[8].
In particular, No. 01-No. 06 are nanotechnologies applied with chemotherapy agents, while nanotechnologies applied with target therapy are No.07, 08, 09; with hormone therapy is No. 12; with the molecule siRNA is No. 13 and with a chemoprevention substance is no. 16.
Some numbers are not included in some analyses because these keywords do not concern anticancer drugs but EGFR, HER2, etc.

The study is conducted by the following steps:

[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] Number 10, 11, 13, 14 and 15 are not included in the figures in next section, because these keywords do not concern anticancer drugs but EGFR, HER2, etc.

- *Step 1*: To map the evolutionary growth of nano 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 application of 16 nanotechnologies is explored by citation analysis.

- *Step 3*: To link specific nanotechnologies with specific cancer field.

Given that not all the nanotechnologies are equally applied in all cancer treatment, we adopt network analysis to link the specific nanotechnology and the cancer field.

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

Moreover if we suppose *j* is the cancer field and *i* is country, its research weight 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 can be written as:

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

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

  Each country may have their own concentrate in certain research fields. 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} .

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

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

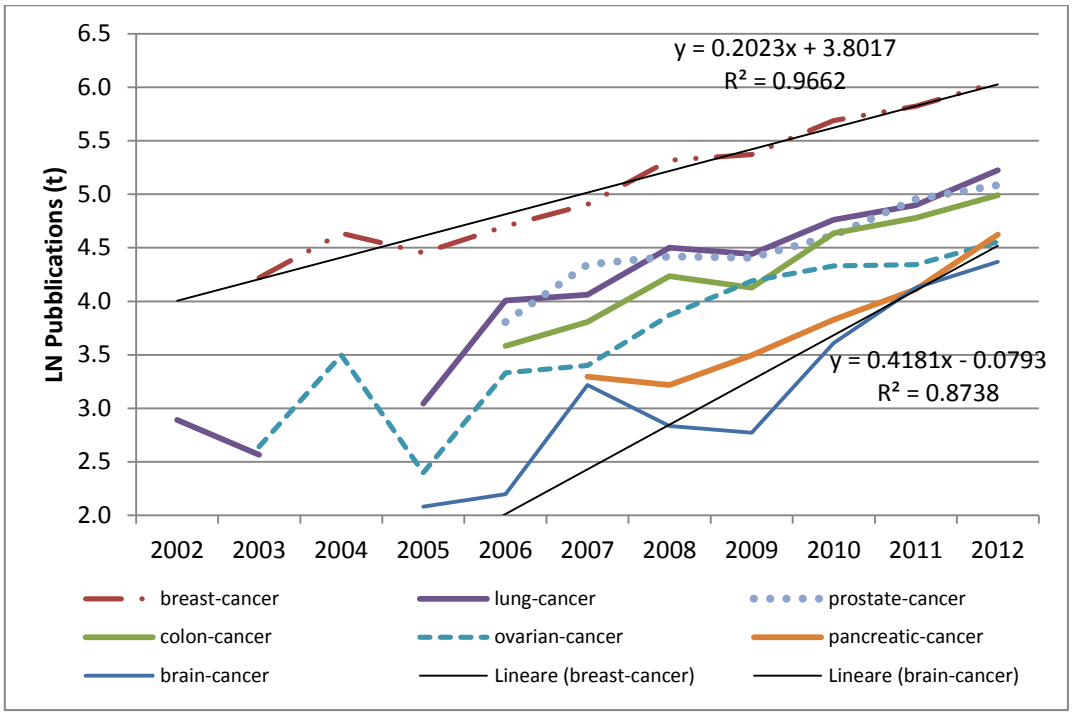
$$\gamma_{ij} = C_{ij} - W_j; \quad j = 1, \dots, n. \qquad (4)$$

High level of index γ_{ij} indicates that the high specialization of the country *i* in the specific research field *j*. $\gamma>0$ 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.

4. Main results and discussions

Figure 1 shows that the number of publications concerning nanotechnology applications in cancer treatments is growing. The highest rate of knowledge growth trends are driven by cancers that have a high mortality rate, such as breast, lung and colon cancer. It is interesting to note that brain cancer and pancreatic cancer had a low activity of scientific production in early 2000, but it is increased sharply in later years. In the long run, there shows a convergence of these trajectories over years. This general trend can be further approved by the citation of nanotechnology in these fields (*see* Figure 1A).

Figure 1: Publications of nanotechnology in cancer treatments per 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.

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 with the highest citation intensity are in brain cancer. Following brain cancer, pancreatic cancer is the second field where nanotechnology has been intensively applied, 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 in Table 1).

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

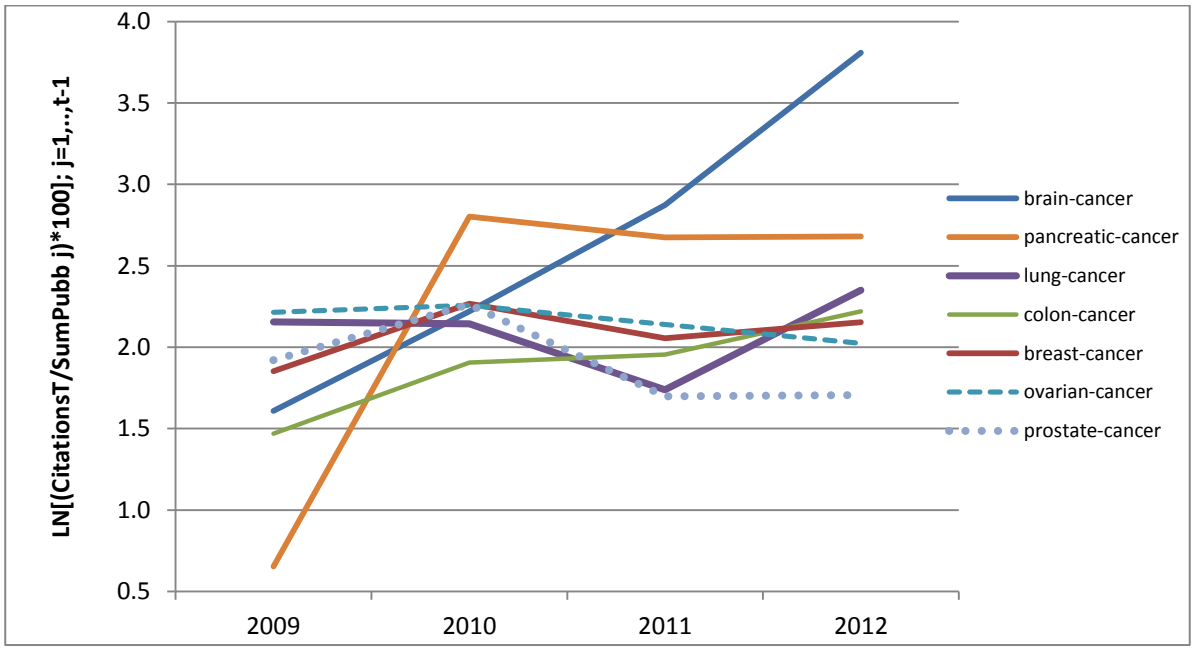
Field	average of nano citation intensity in cancer field (average of 2009-2012)	Ratio of Mortality/incidence
Brain-cancer	19.3%	0.714
Pancreatic-cancer	11.9%	0.949
Ovarian-cancer	8.7%	0.603
Lung-cancer	8.3%	0.843
Breast-cancer	8.1%	0.319
Colon-cancer	6.8%	0.477
Prostate-cancer	6.8%	0.265

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.

Combining the factors of mortality and incidence rate of different cancer fields, it is interesting to observe that cancer fields in which the ratio of mortality to incidence is high all have high nano citation density, and *vice versa*. This result indicates 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 nano application is very high. This reveals that nanotechnology plays a crucial role in these specific cancers (with high mortality rate) because it might represent new technological avenues to find effective therapies in order to increase the survival of patients.

In fact, Figure 2 confirms the high intensive citations of nanotechnology research are applied in brain and pancreatic cancer. This can be confirmed by the Figure 1A.

Figure 2: 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.

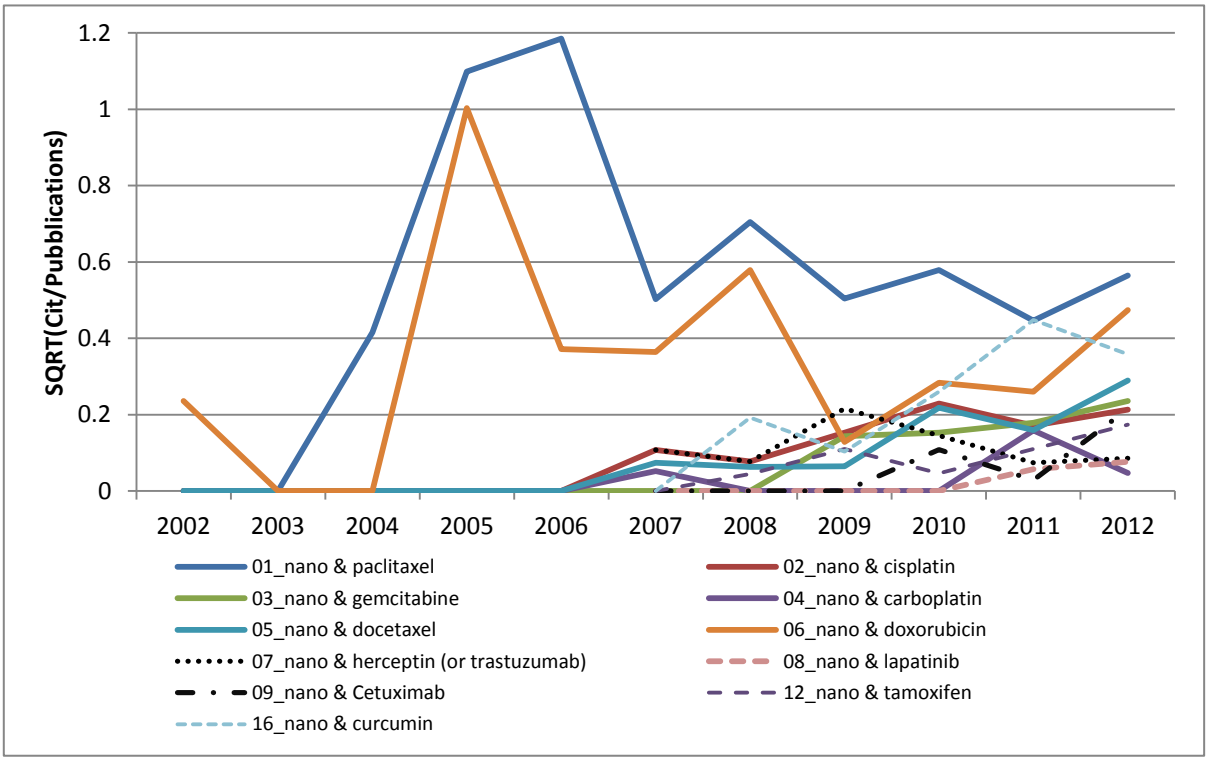
Figure 3 shows the trajectories of main anticancer drugs applied in nanotechnology. This figure displays interesting findings. First of all, the scientific research of nanotechnologies that are applied to chemotherapy agents (i.e. No.01 & No.06) started in 2002-2003, whereas the nanotechnologies that are used in new target therapy (No.07, 08, 09, 12 &16) started later, 2007 or thereabouts. The highest intensity of scientific research is based on nanotechnology with the well-know chemotherapy agent paclitaxel (discovered in US during 1960s) and doxorubicin (discovered in Italy over 1950s). The high growth of these anticancer drugs can be due to broad spectrum of applications of these chemotherapy agents 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. For instance, 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. Paclitaxel albumin-stabilized nanoparticle formulation is approved to be used alone or with other drugs to treat (National cancer institute, 2013):

- 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.

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: docetaxel, gemcitabine and cisplatin.

As far as target therapy is concerned, this is a new technological paradigm to treat the cancer that has generating a revolution in clinical practice (Coccia, 2012b). Growing trends of the association between target/hormone therapy and nanotechnologies are given by cetuximab and tamoxifen. Cetuximab is used for the treatment of metastatic colorectal cancer, head and neck cancer. Tamoxifen is currently used for the treatment of both early and advanced ER+ (estrogen receptor positive) breast cancer in pre- and post-menopausal women. Herceptin was one of the first target therapies of interest for nanotechnology applications to treat cancer; it achieved a peak in 2009, though now there is a declining trend of scientific activity in this technological trajectory. The trend of curcumin associated to 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).

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



Note:
1) Nanotechnologies applied in chemotherapy agents are No. 01-No.06, while nanotechnologies applied in target therapy are No.07, 08, 09, 12 & 16.
2) No. 10, 11, 13, 14 & 15 are not included because the keywords do not concern anticancer drugs but EGFR, HER2, etc.
3) Square root is applied to better represent the values.

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

In particular, figure 4 shows that there are two clusters of nanotechnologies applied to chemotherapy agents, general ones (No. 01 & 06) and specific ones (No.02, 03, 04 & 05). Chemotherapy agent doxorubicin and paclitaxel 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 other chemotherapy agents have reduced spectrum of applications, more focused on specific cancers such as gemcitabine with pancreatic and brain cancer (latter case is also to treat metastases), cisplatin with ovarian, docetaxel with 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, whereas nanotechnologies associated to doxorubicin and paclitaxel are those more frequently cited.

Figure 4: Network of main nanotechnologies applied in different cancer treatment (chemotherapy agent)

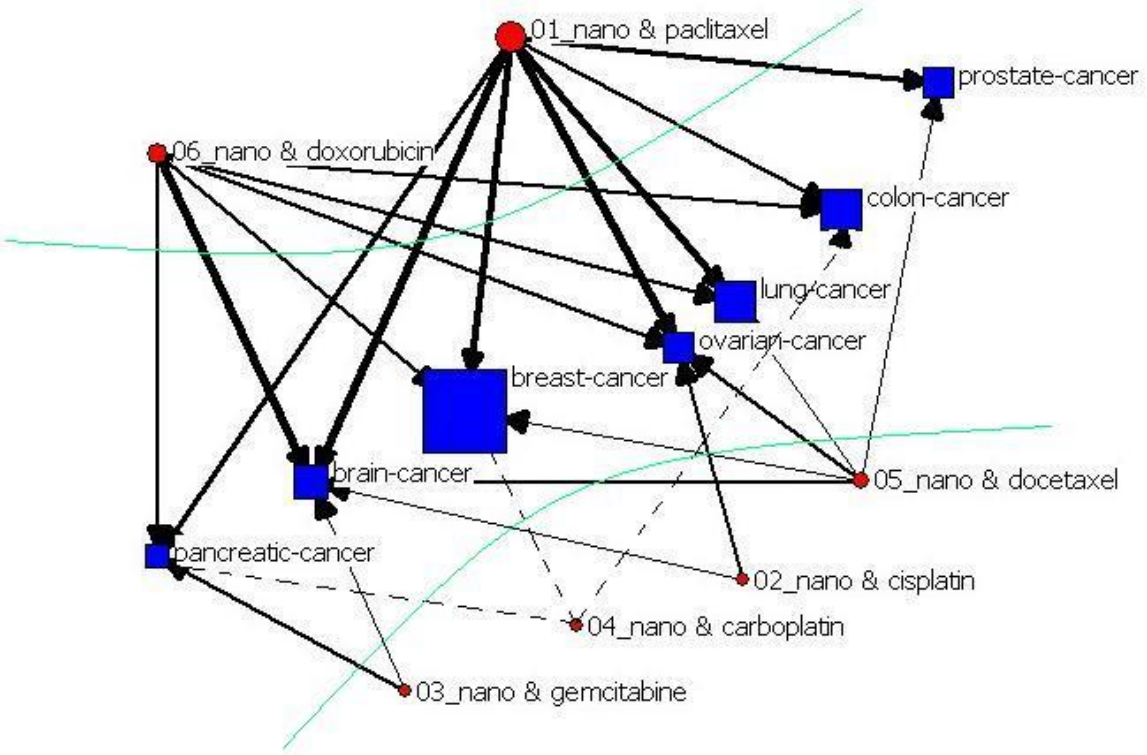
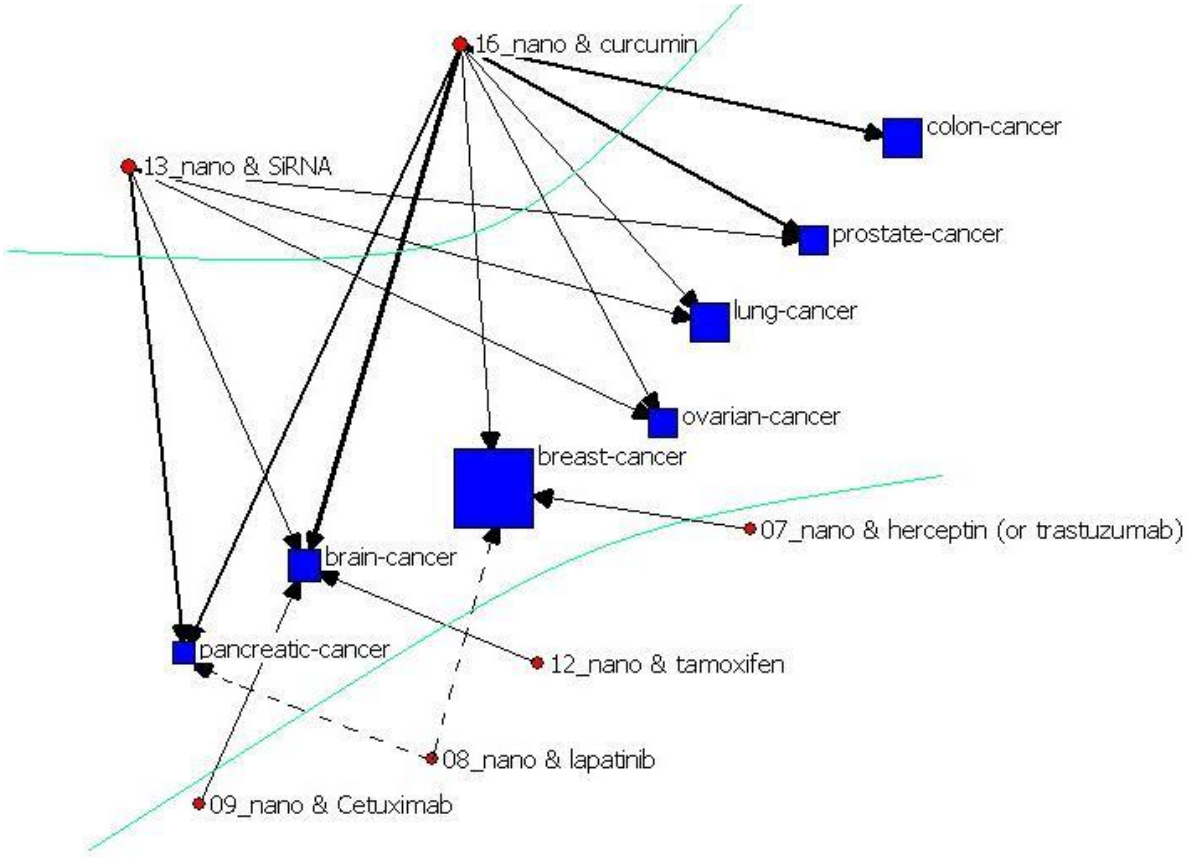


Figure 5, instead, shows similar results for nanotechnologies that use target therapies and other anticancer substances/RNA molecules. Similar to the previous results, Figure 5 presents also two groups of nanotechnologies, i.e. widely applied general target therapy/substance with nanotechnologies and specifically applied ones. The curcumin substance for chemoprevention and siRNA molecules 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 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 there is high uncertainty and complexity to treat brain cancer. As well as a new interesting connection is between lapatinib and pancreatic cancer.

Based on in vitro results, lapatinib may provide clinical benefit in EGFR[9] positive pancreatic ductal adenocarcinoma (Walsh *et al.*, 2013).

As far as target therapy is concerned, breast, brain, lung and colon cancer have a larger volume of research records in these fields.

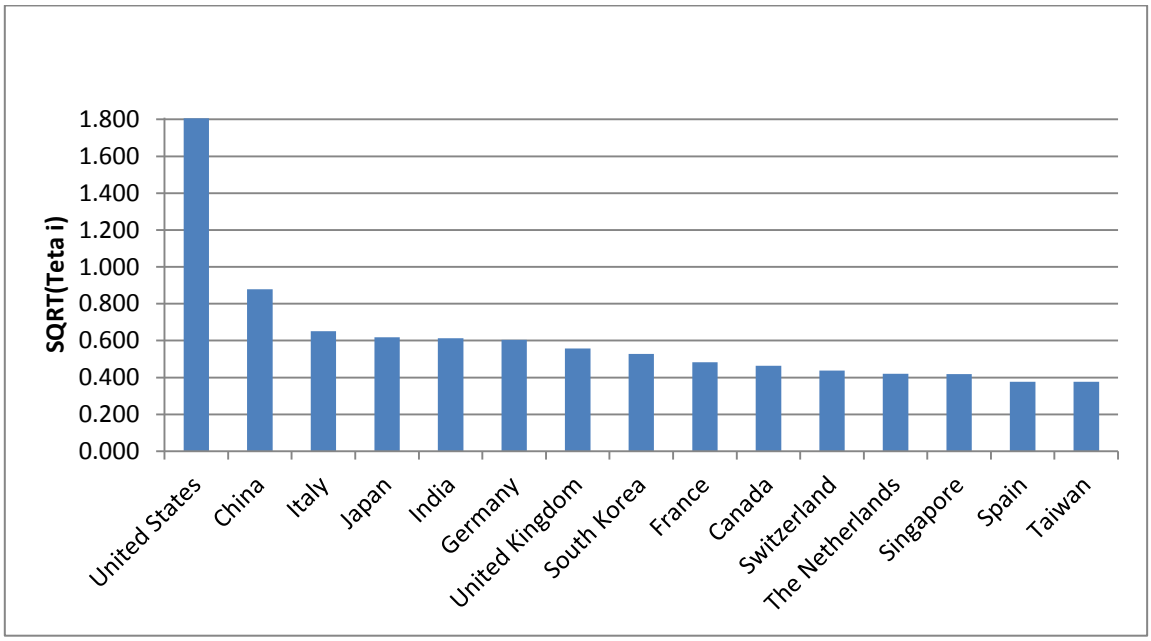
Figure 5: Network of main nanotechnologies applied in different cancer treatment (target therapy)



To explore the origin 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 nanotechnologies in all specific types of cancer.

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

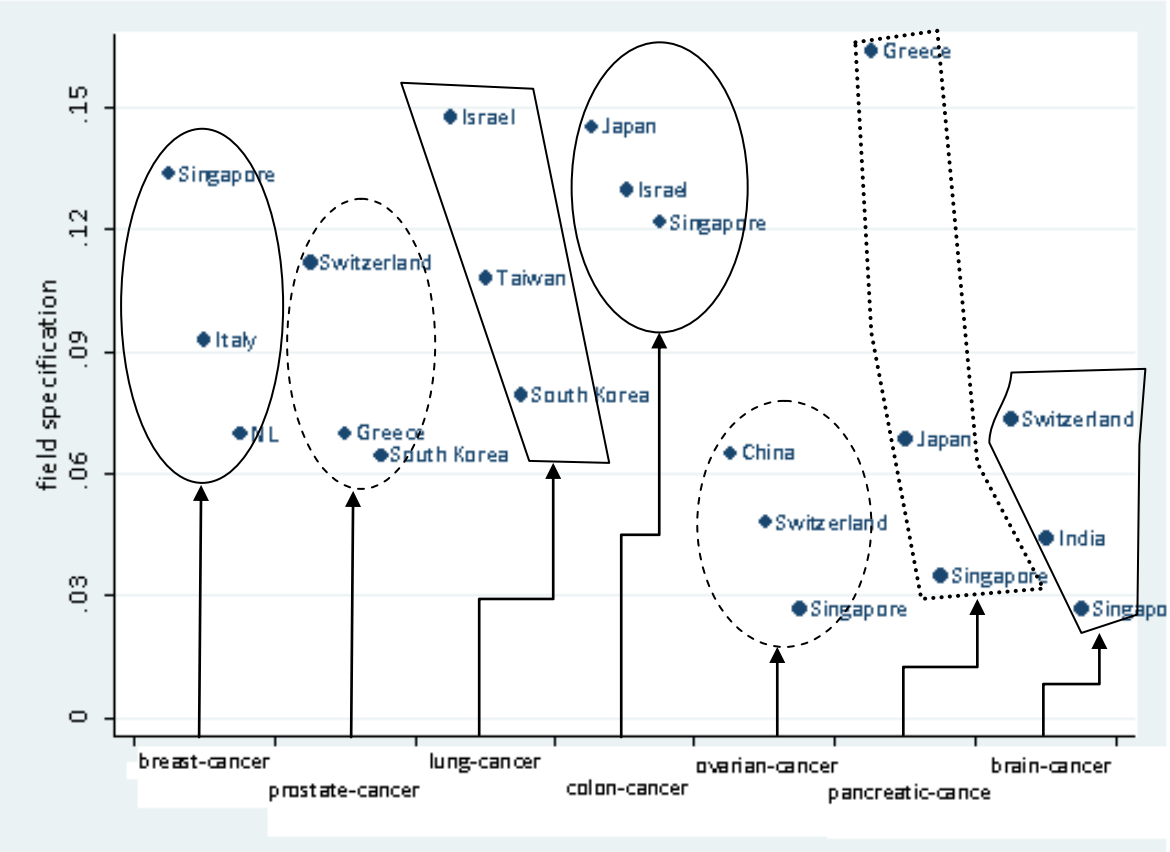
Figure 6: Top 15 high performer countries in nanotechnology applied for cancer treatments (2000-2012)



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

Different from Figure 6 which makes a comparison across countries, 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 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.

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



Note: See detailed calculation equations in Section 3.

5. Concluding observations

The paper analyzes the trajectories of nanotechnologies applied to cancer treatment. Using publication and citation data covering 7 cancer fields and 16 types of nanotechnologies, our study shows that the emerging nano-research fields in biomedicine to treat cancer are growing rapidly over year. There has been a great number of applied research output recording the application of nanotechnologies in the fields of cancer treatment. However, most importantly, nanotechnology opens a new era for cancer field where mortality is high and traditional treatment/approach are not effective enough. In fact, in brain cancer and pancreatic-cancer, although the total research output is low, nanotechnologies seem to play an increasingly important role to find ground-breaking treatments that have high effectiveness and low adverse effects to increase survival rate of patients.

Over the studied 13 years, two technological waves of new anticancer drugs applications *via* nanotechnology have been detected in our analysis. One technological wave (including two types of chemotherapy agents) starts in early 2000 and the other one (including nanotechnologies applied in

both chemotherapy agents and target agents) emerged after 2006.

The network analysis seems to show that there have been both general and specific nanotechnology treatments applied in cancer therapy. This study links the nanotechnologies and cancer fields.
The continuous progress of nanotechnology in biomedicine is supported by high intensity of scientific and technological production growth that accumulates scientific and technical knowledge and spurs the ground-breaking technological trajectories. These new technological avenues might have a pervasive diffusion in biomedical sciences and generate 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 not-too-distant future.

Appendix

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

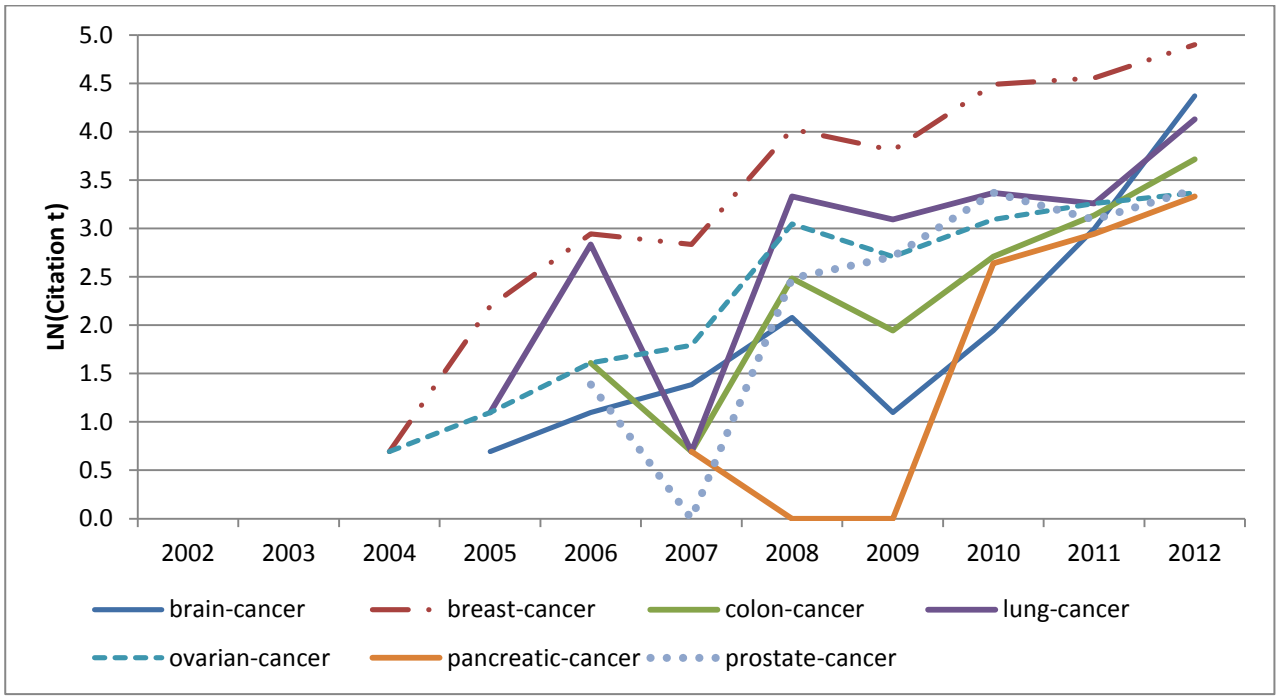
Note: if i is the country and j is the research field (e.g. Breast cancer), the location of the countries in the map is given by the index γ that indicates the high specialization of the country i in the specific research field j

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

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

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.

Figure 1A: 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.

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