



Global Patent Landscape in Breast Cancer Metastasis

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Breast cancer is the most commonly diagnosed cancer in women, with 1.7 million new cases annually and 520,000 deaths globally [1], and metastasis to distant organs is responsible for ~90% of this death. Metastasis is the process by which breast cancer cells spread from the primary tumor to establish colonization at distant organs, such as the bone, lung, liver, and brain. It has been estimated that 85% of patients develop metastasis of bone [2], while 60 - 70%, 50% and 15 - 35% develop metastasis to lung [3], liver [4] and brain [5] respectively.

Despite an increasing trend in breast cancer research, metastasis remains the problem to overcome. Given this situation, it is necessary to evaluate scientific research to establish research policies adjusted to efficiency and effectiveness, and subsequently recommend adjustments to them. Recently, publications trend on breast cancer-originated metastasis was determined; it is notable that the publications trend concerning bone metastasis was above the trend of lung metastasis, whereas the trends of liver and brain metastasis were very similar [6]. It is also important to emphasize that in the last years the production of research publications tries to fulfill the magnitude of the problem.

On the other hand, the patent system allows carrying out various studies where the tendency of patent applications in a certain area of interest is analyzed. This analysis allows knowing the status of a certain scientific-technology area, including who are the leading countries, companies and inventors in a certain field. With this, duplication of efforts in scientific research is avoided. However, trends regarding patents on metastasis in breast cancer have not been addressed. Therefore, the objective of this study is to identify recent patents on breast cancer metastasis with the purpose that, based on the analysis, institutions, companies and scientists promote research policies that do not lead to duplication of efforts by continuing to investigate something that has already been addressed. In addition, a list of the most cited patents in this area is provided.

Materials and Methods

We obtained the patent documents in the databases of patent offices in the US (www.uspto.gov/patents-application-process/search-patents), Europe (worldwide.espacenet.com/advancedSearch?locale=en_EP), China (211.157.104.77:8080/sipo_EN/search/tabSearch.do?method=init), Japan (www4.j-platpat.inpit.go.jp/eng/tokujitsu/tjkt_en/TJKT_EN_GM201_Top.action) and Korea (engpat.kipris.or.kr/engpat/searchLogina.do?next=MainSearch) by using the keywords approach related to breast cancer metastasis. To do this, we executed the search strategy in the title/claims/summary sections by using the following terms: (metast*) and [(breast invasive ductal carcinoma) OR (infiltrating duct carcinoma \$) OR (mammary ductal carcinoma \$) OR (breast cancer) OR (breast neoplasm \$) OR (breast tumor \$ r \$) OR (human mammary neoplasm \$) OR (human mammary carcinoma \$)]; where \$ = any character, * = two or more character. Additionally, the data were recorded to obtain: a) patent trend distribution, b) top applicants, c) top countries, d) main international patent classification codes and e) patents with highest number of citations.

Results and Discussion

A total of 6574 patents (patent families) were obtained for the period 1998 - 2007, observing an increasing trend (Figure 1). The top ten countries in the patent claim are shown in table 1, where the US (2597) was the leader followed by Australia (1031), China (196), Germany (111) and South Korea (91). Additionally, figure 2 shows the top ten of patent applicants. With the exception of Nerviano Medical Sciences (Italy) and Novartis (Switzerland), all the assignees are from the United States. Four are universities (University of Texas, University of California, University Johns Hopkins and Dana Farber Cancer Institute) and one is a government entity (US Health). Likewise, top ten inventors are shown in figure 3; with the exception of Sui Yi Kwok and Bing Lou Wong (both from Taiwan) all the inventors are from the United States.

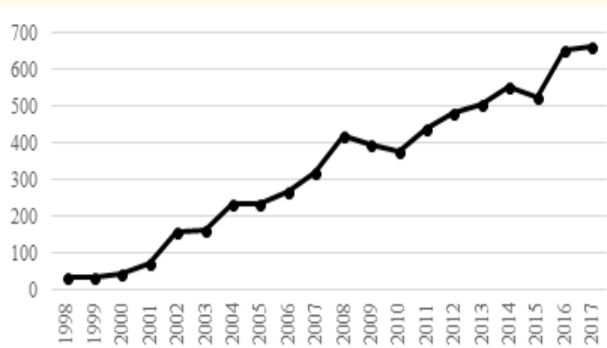


Figure 1: Patent trend distribution analysis based in breast cancer metastasis, 1998-2017. $p > 0.001$.

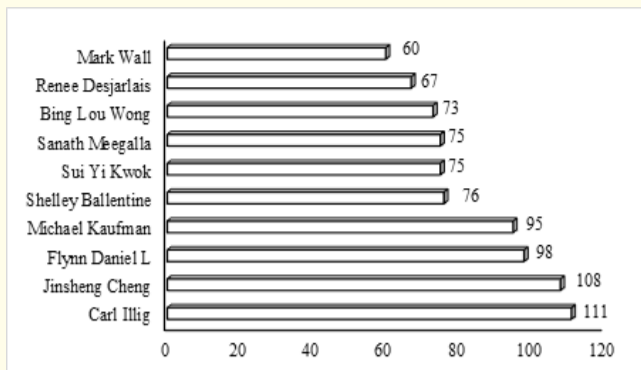


Figure 3: Top ten of inventors with patents on breast cancer metastasis, 1998-2017.

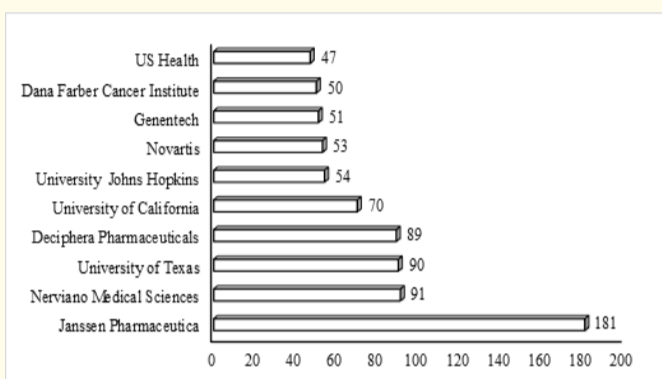


Figure 2: Top ten of applicants with patents on breast cancer metastasis, 1998-2017.

Country	1998-2002	2003-2007	2008-2012	2013-2017	Total
USA	101	482	821	1193	2597
Australia	93	206	301	431	1031
China	0	8	69	119	196
Germany	1	11	51	48	111
South Korea	2	14	23	52	91
England	7	14	22	45	88
Canada	7	14	27	24	72
Japan	4	9	13	33	59
France	2	9	15	32	58
Switzerland	4	9	14	16	43

Table 1: Top ten countries with patents on breast cancer metastasis, 1998-2017.

On the other hand, main International Patent Classification codes on breast cancer metastasis are shown in table 2. Two IPC codes (A61P35/00 and A61P35/04) were relevant for drugs based

on chemical compounds; one IPC code (A61K39/395) was relevant for oncology immunotherapy; and one IPC code (C12Q1/68) was relevant for testing processes involving nucleic acids.

IPC	Definition	1998-2002	2003-2007	2008-2012	2013-2017	Total
A61P35/00	Specific therapeutic activity of chemical compounds or medicinal preparations; antineoplastic agents	170	343	926	721	2150
C12Q1/68	Measuring or testing processes involving enzymes, nucleic acids or microorganisms; involving nucleic acids	91	238	378	382	1089
A61K39/395	Medicinal preparations containing antibodies	47	165	392	357	961
G01N33/574	Investigating or analysing materials by specific methods for cancer	85	200	234	334	853
A61P35/04	Specific therapeutic activity of chemical compounds or medicinal preparations; specific for metastasis	74	151	279	174	678

Table 2: Main International Patent Classification codes on breast cancer metastasis, 1998-2017.

Table 3 shows the twenty leading patents with the highest number of citations about breast cancer metastasis. Interestingly, of the twenty most cited patents twelve are chemical compounds, two of micro-RNA therapy (miR-145, miR-21, miR-155, miR-10b), and one of immunotherapy (macrophages and/or other antigen presenting cells sensitized with heat shock proteins non-covalently bound to peptide complexes and/or antigenic components). It also highlights that eight patents present protein kinases as targets for drugs (Aurora-2, GSK-3, ROCK, JAK, Cdc7, AKT, PAK4, PLK, CK2, KDR, MK2, JNK1, pim 1 and nek 2).

The evaluation of the activity in patents, in comparison with the analysis of scientific publications, will allow to determine which have been the areas already studied, and consequently to determine the research gaps that need to be addressed. This study analyzed the patents related to breast cancer metastasis obtaining some important points about the trend in this area, e.g. leading countries and institutions/enterprises, and main technical fields addressed (through the patent classification system).

Patent	Title	Applicant	Inventors	Cites
US6057105 [7]	Detection of melanoma or breast metastasis with a multiple marker assay	NGI Cancer Tech	Hoon., <i>et al.</i>	184
US20030198970 [8]	Genostics	Genostic Pharma	Roberts., <i>et al.</i>	176
US5985270 [9]	Adoptive immunotherapy using macrophages sensitized with heat shock protein-epitope complexes	University of Fordham	Srivastava., <i>et al.</i>	142
US6653301 [10]	Pyrazole compounds useful as protein kinase inhibitors	Vertex Pharma	Bebbigton., <i>et al.</i>	136
US20040077601 [11]	Methods and compositions relating to isoleucine boroproline compounds	Point Therapeutics	Adams., <i>et al.</i>	122
WO2010129053 [12]	EGFR inhibitors and methods of treating disorders	Dana Farber Cancer Institute	Gray., <i>et al.</i>	119
US20090203690 [13]	5-substituted indazoles as kinase inhibitors	Abbott Lab	Akritopoulou-Zanze., <i>et al.</i>	110
US6037129 [14]	Multi-marker RT-PCR panel for detecting metastatic breast cancer	University of Soutj Carolina	Cole., <i>et al.</i>	108
US20100029610 [15]	Heteroaryl compounds and uses thereof	Avila Therapeutics	Singh., <i>et al.</i>	106
US6291504 [16]	Acylsemicarbazides and their uses	Du Pont Pharmaceutical	Nugiel., <i>et al.</i>	98
US6100248 [17]	Method of inhibiting cancer growth	Golub., <i>et al.</i>	Golub., <i>et al.</i>	94
US20050148603 [18]	Compositions useful as inhibitors of protein kinases	Jimenez., <i>et al.</i>	Jimenez., <i>et al.</i>	89
WO2007016548 [19]	Micro-RNA-based methods and compositions for the diagnosis, prognosis and treatment of breast cancer	University of Ohio	Croce and Calin	86
WO2004016597 [20]	Protein kinase inhibitors and uses thereof	Vertex Pharma	Cochran., <i>et al.</i>	85
US20080076674 [21]	Novel oligonucleotide compositions and probe sequences useful for detection and analysis of non-coding RNAs associated with cancer	Litman., <i>et al.</i>	Litman., <i>et al.</i>	81
WO2009140128 [22]	Compounds and compositions as kinase inhibitors	IRM	Albaugh., <i>et al.</i>	77
US20050137201 [23]	Compositions useful as inhibitors of protein kinases	Aronov., <i>et al.</i>	Aronov., <i>et al.</i>	75
US20050112630 [24]	Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling	Shaughnessy., <i>et al.</i>	Shaughnessy., <i>et al.</i>	75
US20100215743 [25]	Composition and drug delivery of bisphosphonates	Leonard TW	Leonard TW	72
US20100249092 [26]	Heteroaryl compounds and uses thereof	Avila Therapeutics	Singh., <i>et al.</i>	64

Table 3: Twenty leading patents with the highest number of citations about breast cancer metastasis, 1998-2017.

Due to the lack of trend studies on patents and breast cancer, it is difficult to make a comparative analysis between countries and companies. However, since patents are generally linked to scientific publications, it could be established that the trends of countries between patents and publications are very similar. In this sense, three studies related to diet [27], reconstructive surgery [28] and imaging [29] in breast cancer established that the leading countries in scientific publications are those included in this study, including the USA. The only study, to the knowledge of the author, that involves the behavior of different countries in terms of patents and breast cancer is that described by Anaya-Ruiz and Perez-Santos, which shows the behavior in patents about gene therapy in breast cancer [30]. This work represents the first patentometric assessment of breast cancer metastasis. Based on the analysis of the results of

this study, the policy makers of research could make new designs of research priorities in terms of breast cancer metastasis, and as a consequence, new policies for patent protection [31].

Conclusion

There is an increasing interest in the development and protection through patents in the area of breast cancer metastasis. USA, Australia, China, Germany and South Korea were the jurisdictions of most important countries in the subject. Likewise, their inventors and US companies were the most relevant.

Conflict of Interest

The author declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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