Genetic polymorphism in endometriosis: Trends in scientific production

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ABSTRACT. Endometriosis is characterized by the presence of endometrial tissue located outside the uterine cavity. The prevalence is around 6% to 10%. Regarding etiopathogenesis, several theories are accepted, but alterations in the molecular biology of the endometrium seem to be fundamental for the development of endometriosis. Women with the disease may be asymptomatic or have complaints of dysmenorrhea, dyspareunia, chronic pelvic pain and/or infertility. Although the definitive diagnosis requires a surgical intervention, preferably by video laparoscopy, several findings in the physical, imaging and laboratory examinations can already predict, with a high degree of reliability, that the patient presents endometriosis. Polymorphism analysis has contributed to a better understanding of the genetics of endometriosis. The objective of this study was to characterize the scientific production of genetic polymorphisms in endometriosis until 2013 from a Scientometric perspective. For this, a bibliographic survey was performed on the Scopus site, using the words "polymorphism * genetic * AND endometriosis * molecular OR * marker * AND endometriosis *. It was analyzed the articles: type of publication, number of articles/year, authors, areas, journals, impact factor of the most published journals, among others. As a result, there was an increase in the number of publications on endometriosis and polymorphisms over the years, mainly in developed countries. It was observed a relevant association with infertility, ovarian cancer and endometrioma. Many studies have evaluated genes like GSTM1 and PROGINS.

Key words: Endometriosis; Genetic polymorphisms; Molecular markers; Scopus; Scientometrics

INTRODUCTION

Endometriosis is characterized by the presence of functional tissue located outside the uterine cavity, most commonly in the pelvic peritoneum, in the ovary and rectum, and more rarely in the pericardium, pleura and central nervous system. (Nácul and Spritzer 2010). The studies show a prevalence of up to 20% of women of reproductive age (Bricou et al., 2008) and 30% to 50% of infertile women with endometriosis. (Jacobson et al. 2002).

The etiopathogenesis is still not well established, but the evidence indicates that the combination of genetic, hormonal, and immunological factors could contribute to the formation and development of ectopic foci of endometriosis. (Kennedy et al., 2005)

The most accepted theory to explain the development of endometriosis is the implantation theory described by Sampson in 1927. According to this author, reflux of endometrial tissue through the Fallopian tubes during menstruation would occur, with subsequent implantation and growth in the peritoneum and ovary (Nácul and Spritzer 2010). A recent study, confirming Sampson's theory, found that the distribution of endometriosis implants is asymmetrical and related to both the abdominopelvic anatomy and the flow of the peritoneal fluid (Bricou et al., 2008).

One of the aspects discussed about this theory is that although 70 to 90% of women have retrograde menstruation, only a minority will develop the disease. This suggests that other genetic, hormonal, or environmental factors could determine a greater susceptibility to developing the disease. Increased expression of genes involved in the cellular apoptosis mechanism may increase the survival of these cells within the peritoneal cavity which, interacting with adhesion molecules, will adhere to the peritoneal surface. (Bricou et al., 2008; Morsch et al., 2009). Endometriosis has been related to polymorphisms in genes *p53, GSTM1, GSTT1, Reβ, PROGINS e CYP1A1* (Bianco et al., 2011).

The current trend is the search for strategies that can identify potential genes that cause the disease. Incidence data on endometriosis are consistent with polygenic or multifactorial inheritance; it is believed that several genes are involved, or multiple alleles exist at the same locus. Other evidence supporting polygenic inheritance is the increased severity of the disease in cases of endometriosis observed in women of the same family. The analysis of polymorphisms has contributed to the better understanding of the disease as to its genetic makeup. These polymorphisms are related to enzymes that metabolize drugs, growth factors, and hormone receptor genes. There is no specific gene to investigate endometriosis, however, there are some associations described in the literature (Freitas and Silva 2013).

To quantify and qualify massively generated publications, such as publications using endometriosis and polymorphisms, the number of researchers analysing in a Scientometric manner is increasing. (Carneiro et al., 2008; Quixabeira et al., 2010). According to Nonato (2003), Scientometric was defined in the late 1970s as "the quantitative research of all things that pertain to science, to which numbers can be attributed." According to Vanti (2011), Scientometric can be defined as a quantitative evaluation of scientific and technological activities, with the main objective of focusing on the number of methodologies, or even the structure of several research centers. Its importance is due to its ability to analyze the quantitative aspects related to the generation, propagation and use of scientific information about a country, a scientific community, or an institution. (Groesser 2012; Gupta 2012).

The progress of the knowledge about endometriosis is unquestionable, therefore a Scientometric analysis is necessary to evaluate its development, to verify the tendencies of studies and to indicate the number of articles in a certain period, countries, types of periodicals, authors, among others. The objective of this study was to characterize the trends of scientific production on endometriosis and polymorphisms

METHODOLOGY

For the quantitative analysis of studies about endometriosis and genetic polymorphisms, the bibliographic production was used as an indicator of the results obtained in the last 32 years. The data were obtained through the Scopus database, using the keywords "polymorphism * genetic * AND endometriosis * OR * marker * AND endometriosis * ". The use of the asterisk indicates that any termination of the word can be accepted, guaranteeing the search for words in the singular, plural and derived. We used only the compound form because

separately the terms can indicate a huge variety of works unrelated to the interrelated subjects, that do not fit the objectives of this study. The period of the research was from 1981 to 2013, since there are only articles published since 1981. Scopus was used because of its comprehensiveness regarding the number of publications and the quality of indexed journals.

From the selected publications, the following information was collected: 1. Type of document published (experimental, review); 2. Year of publication of the article; 3. Periodical in which the article was published; 4. Impact factor of the journal that published the article; 5. Name of the authors of the work; 6. Main author index H; 7. Area of knowledge in which it fits; 8. Institution to which the authors are affiliated; 9. Countries where the studies were carried out; 50 10. Language in which the article was published; 11. Associations with endometriosis (infertility, ovarian cancer); 12. Main genes covered.

The impact factor (IF) of the articles used in the analyses was obtained from the Journal Citation Reports (JCR) for the most recent year cited (Impact Factor Search 2014). The IF is an indicator used to calculate the average number of citations received by a scientific journal and is obtained by the ratio between the number of times the journal was cited and the number of articles it has published in a given period of time, usually two years. The purpose of the use of this indicator is to discover the impact of journals in the scientific Community. (Groesser 2012; Thomaz et al., 2011).

The H-index of a researcher is defined by the number of articles published by the researcher, which obtain citations greater than or equal to that number. For example, when we say that a researcher's H-index is ten, it means that he has at least ten published articles, each with at least ten citations (THOMAZ et al, 2011).

Currently the Scopus database automatically calculates the H-index of the searcher. Information such as associations with endometriosis (infertility, ovarian cancer) and the main genes addressed in the studies were obtained by reading the abstracts. Thirty-eight articles do not provide the same and, therefore, were excluded in these evaluations. Of the 625 scientific papers that appeared in the search with the chosen keywords 116 did not address the topic endometriosis and, therefore, was excluded. For example: "Diagnosing fibromyalgia and myofascial pain syndrome: A guide". Then the data of the works were tabulated and organized in an Excel® spreadsheet according to each variable of the research, as already mentioned. From then on, the tables were set up separately and descriptive statistics were used to present the results. To evaluate the association between the number of publications and year and the IF and year, we used the Spearman correlation. A significance level of 0.05 was used for all analyses. The Bioestat 5.0 program (Ayres et al., 2007) was used to perform the statistical analyses.

RESULTS AND DISCUSSION

According to the survey, 625 papers published between 1981 and 2013 were found using the words "polymorphism * genetic * AND endometriosis * OR * marker * AND endometriosis *". Of these, 116 were excluded because they did not really address the issue.

In a total of 509 articles, 63 (12%) were revisions and 427 (84%) were original articles, making a total of 96% and demonstrating that there was interest in studying endometriosis allied to polymorphisms. The other 19 articles that represent 4% of the research are letter, editorial, chapter book, note and press article. Studies in different areas have shown that review studies are less frequent than experimental or descriptive studies However, despite the low frequency of review articles, these are often the articles with the highest number of citations. (Quixabeira et al. 2010; Carneiro et al. 2008). According to Figure 1, the number of publications increased sharply from the year 2000, with a slight decline in 2004 and peak in 2013 (67 articles). The analyses showed a strong correlation between the year and the number of publications ($r = 0.9566$, $p<0.0001$).

Despite the numerous complex diseases well known today, the result of a century of clinical observations and discoveries, endometriosis seems to have been marred by the history of medicine for a long period of time. Many Gynecological diseases can be recognized in the writings of Hippocrates (460 BC-370 BC), but this was not the case with endometriosis. The scarcity of observations or information on the disease is so striking that there is no reference to endometriosis in important encyclopaedias of medical history, such as Cambridge World History of Human Disease, edited by Cambridge University in 1993.

In the 1980s and 1990s, advances in the fields of immunology and genetics deepened basic research on endometriosis and have now become an inexhaustible source of studies, projects, and publications (Podgaec 2014). Cornillie (1990) introduces the concept of deep infiltrating endometriosis, differentiating it from

superficial ovarian endometriosis. The search for molecular markers for the diagnosis of endometriosis and for better staging of the disease had great momentum in this period. The refinement of surgical techniques has also evolved considerably, with the introduction of ever more delicate instruments and the introduction of robotics. Following the publication by Vincent Knapp (1999) of "How old is Endometriosis", which was intended to fill the void in the history of the disease, there was a renewed interest in determining when endometriosis was identified as a distinct disease. With the beginning of the 21st century, year 2001, came the evolution in the non-surgical diagnosis of lesions of deep and infiltrating endometriosis. Some groups in Europe and America have developed important works in magnetic resonance imaging, transvaginal ultrasound (USTV) and endorectal ultrasonography. Brazil has excelled in this field with relevant publications placing the USTV as a method of high accuracy in the diagnosis of lesions of deep retro cervical endometriosis and rectosigmoid endometriosis. (Podgaec 2014) Recently, the Nezhat brothers published in (2012) the article Endometriosis: ancient disease, ancient treatments; a very in-depth study on the history of the disease through which it was possible to show, through observations, reports and images, the presence of signs and symptoms suggestive of endometriosis dating back 2,500 years. In 2013, the World Endometriosis Society published the first consensus on endometriosis, seeking to delineate the main points in relation to diagnosis and conduct, in front of the carriers of the disease. In the evaluation of the number of journals and the total of articles, it was observed that 160 different magazines published on the subject studied. However, only eight journals obtained several publications equal to or greater than 11 papers, making a total of 211 articles, corresponding to 42% of publications (Table 1). In genetic studies correlated with endometriosis, of the journals with a high publication rate, Fertility and Sterility published 69 articles, corresponding to a total of 33% of the publications.

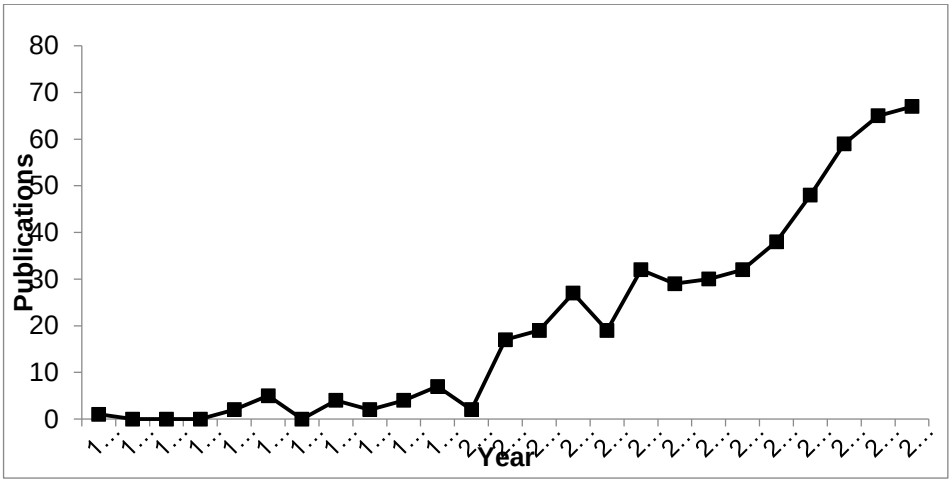

Figure 1. Number of articles published during the 32 years in genetics using endometriosis and polymorphism indexed to Scopus (r = 0.9566, p <0.0001)

Table 1. Journals with a publication frequency greater than or equal to 11 articles.

Journals	n	%
Fertility and Sterility	69	33
Human Reproduction	35	17
Molecular Human Reproduction	31	15
European Journal of Obstetrics Gynecology and Reproductive Biology	23	11
American Journal of Reproductive Immunology	17	8
Gynecological Endocrinology	13	6
Journal od the Society for Gynaecologic Investigation	12	6
Archives of Gynecology and Obstetrics	11	5
Total	**211**	**42**
Others	286	58

Grand total	**497**	**100**

Fertility and Sterility is an international journal for obstetricians, gynaecologists, sterile nurses, urologists and others who treat and investigate problems of infertility and reproductive human disorders. The journal publishes original scientific articles in clinical and laboratory research relevant to reproductive endocrinology, urology, andrology, physiology, immunology, genetics, contraception, and menopause. Encourages and supports basic and clinical research, facilitates, and promotes excellence in professional education in the field of reproductive medicine (Fertility and Sterility 2015).

Like the seven ranked journals, Fertility and Sterility, it presents a multidisciplinary approach, which confirms the importance of endometriosis in different areas of knowledge. As for the impact factor of the periodicals used in the analyses, an average value of 3,481 (± 2,916) was found, ranging from 0.07 to 29.64. The magazine with the largest number of publications, Fertility and Sterility, has a IF of 4.29, which is close to the average IF. Besides it, only two of the most published journals, Human Reproduction and Molecular Human Reproduction have a high IF, above three. Thus, the results show a considerable impact on the researched subject in the scientific community. There was no significant correlation between the IF and the year ($r = -0.0694$ and $p = 0.1114$).

Scientometric aims at the advancement of knowledge and seeks to relate this to social issues and public policies. It has, therefore, a multidisciplinary character. Its goal is to generate information and discussions that contribute to overcoming the challenges characteristic of modern Science. (Shtovba e Shtovba 2013)

Beyond any definition or concept, it is known that Scientometric has great potential for application, arousing the interest of governments and research institutions. Indexes of journals as an impact factor (IF) have become an important source of information for historians, sociologists and other researchers interested in the science (Silva et al. 2001). They are important since they are part of the main criteria for choosing the journals that make up the Scopus database, which also considers the periodicity and accessibility of a journal.

The concept behind citation indexing is very simple: by recognizing that the value of information is determined by those who use it, the best way to measure the visibility of a work is by calculating the impact it has on the scientific community. When using or citing a source, the researcher determines the influence of the idea of that author on a body of knowledge (Vanti 2011). Therefore, although for some authors the number of publications, citations and their combinations are not an indicator of the quality of a scientific work, the IF remains an important Scientometric index. (Groesser 2012; Tirgar et al. 2013).

Of the 160 different authors who published the articles analyzed in the present survey, 11 published fifteen or more articles on endometriosis and polymorphisms between 1981 and 2013. These 11 together made up a total of 20% of all publications, with Tsai, FJ, Christofolini, DM and Kennedy, S. published 23 articles, Hsieh, Y.Y. and Barbosa, C.P. published 22 articles and Bianco, B. and Chang, C.C. published 20 articles (Figure 2). Therefore, no author has stood out as to the number of publications.

As for the H index of the authors of the published articles, an average value of 21.04 (± 15.30) was found, varying from 1 to 82. The author Martin, N.G. presented the highest H index among all published authors. His index is 82 and means that he has at least eighty-two published articles, each with at least eighty-two citations. Taking into account that the greater the number of articles of great interest published by the researcher, the greater number of citations reached and the higher will be its H index, we conclude that this researcher presents a good academic-scientific quality and productive capacity (Thomaz et al. 2011). Martin, N.G. is Australian and has published only seven articles, among all found in the research which suggests that they are of great interest. His institution is the Queensland Institute of Medical Research, the fourth in publication in the survey.

With the increasing demand for inputs to finance scientific research, it has become necessary to create mechanisms for the evaluation of scientific academic quality, as a way to give prestige to institutions and individuals capable of producing leading research, thus guaranteeing a profitable investment of the agency's research (Bornmann and Daniel 2009).

The H index is one such mechanism and was described in 2005 by physicist Jorge E. Hirsch of the University of California as a tool to determine the relative quality of theoretical physicists (Hirscht 2005). Quickly, the H index gained prominence in other disciplines and became widely used in scientific circles. Many authors consider it not only the safest way to measure the scientific quality of the researcher, but also a good tool to evaluate the regularity of production and predict future scientific performance, as it combines productivity with impact. This is the number of articles with quotations greater than or equal to that number. Thus, it aims to

quantify the productivity and impact of scientists based on their most cited articles. (Kellner and Ponciano 2008; Kulasegarah and Fenton 2010).

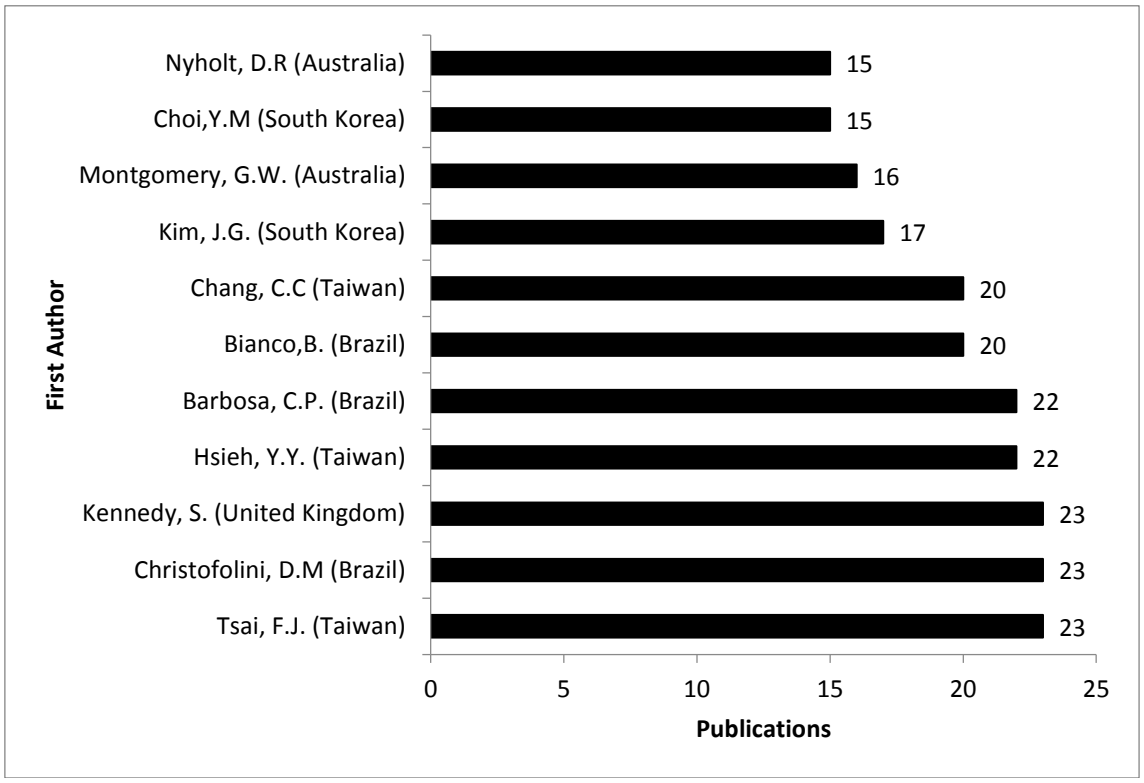

Figure 2. Name of eleven main authors who present fifteen or more publications on the subject searched.

Hirsch, in 2005, argues that individuals with similar H indices are also comparable in terms of scientific impact, even when the number of articles or total number of citations of both are very diverse. Differently, when we compare two individuals (of equal scientific age), with equal numbers of publications or citations, and with very disparate H indices, the one with the highest H index is probably a more talented researcher. However, like any simplistic attempt to categorize or classify a researcher's output by a single number, the H-index is far from perfect and faces a number of criticisms. Among these, besides the usual ones that cannot be characterized as a researcher by a number, are: self-citation, the distinction between active and inactive scientists, depending on scientific age, differences between areas, etc. (Engqvist and Fronmen 2008).

The articles were published in seven different scientific areas, according to the classification of SCOPUS. The most published articles related to endometriosis and polymorphisms in the analyzed period were Medicine (65%) and Biochemistry, Genetics and Molecular Biology (23%). (Figure 3). This suggests that, despite the multidisciplinary interest, endometriosis had an impact, mainly in the field of Medicine and Biochemistry, Genetics and Molecular Biology, which together represent 88% of publications. In the area of Medicine it is easy to understand why the high rate. Despite being one of the most studied diseases in gynecology, some aspects continue to be the object of research, highlighting the search for its pathogenesis (Acién 2013).

Many studies have been carried out in an attempt to identify the immunological, genetic alterations or even the responses to environmental contaminants that may be present in patients with endometriosis. In an attempt to establish a non-invasive diagnosis and, thus, an earlier treatment, more and more studies have been conducted to evaluate possible inducer/trigger factors of this disease (Bellelis et al., 2014).

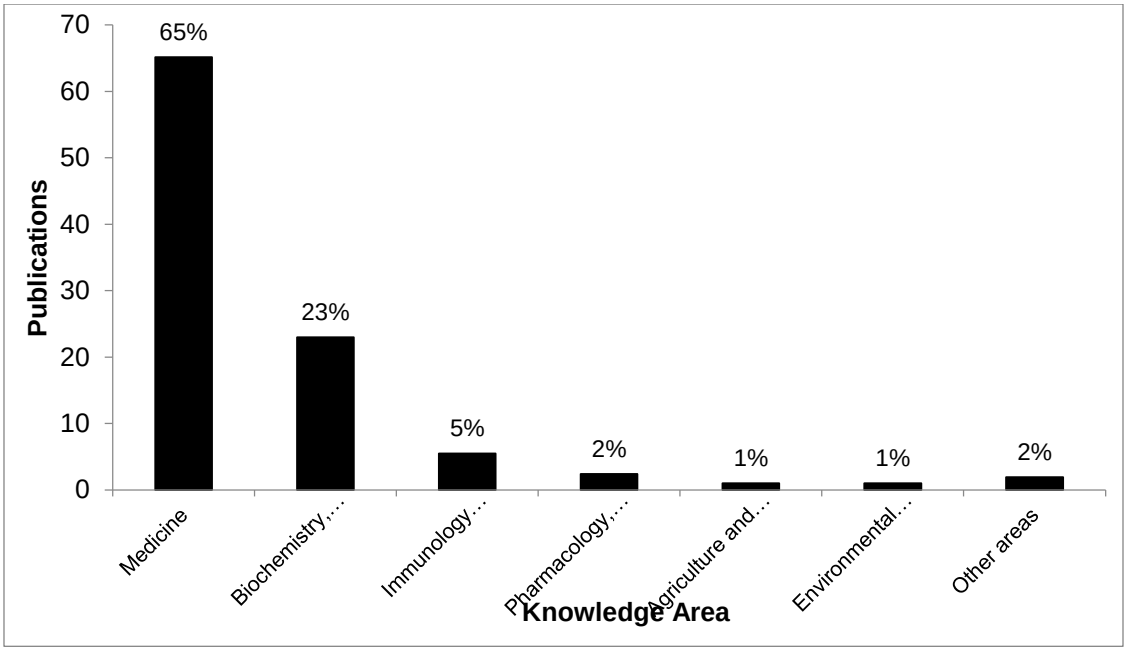

Figure 3. Main scientific areas of publication of studies related to endometriosis and polymorphism between 1981 and 2013.

As for the institutional affiliation of the authors, there is a great diversity with a total of 160 different institutions. However, only six of these institutions have published 15 or more articles and represent 24.75% of all publications. The China Medical University Hospital Taichung published 30 articles that correspond to 5.89% of the total, the Nuffield Department of Clinical Medicine published 26 articles that correspond to 5,10% of the total (Figure 4).

The institutions with the highest and the lowest number of published articles are Chinese. The second institution of the ranking, British; the third, Brazilian; the fourth, Australian and South Korean fifth. This shows that in addition to the diversity of institutions we also have a diversity of countries that study endometriosis, that is, in addition to the traditional countries such as the United States, the European Union and Japan, data are included for China and India, with Brazil, form the trio of emerging countries with the potential to progress in the application and generation of knowledge (Contini and Séchet 2005).

One of the indicators for the progress of science and technology and its prospects is to verify how much the countries invest in the area. They are financial resources for the payment of qualified human resources, construction and maintenance of infrastructure, laboratory equipment and operating expenses with inputs for research, technical travel, publications, and communication. As for investments in research and development, the changes are not as significant. The three major blocs (North America, Europe and South Asia) remain absolute leaders, with 94% of the world's expenditure on research and development (Contini e Séchet 2005).

We know that the recent evolution of world scientific research is marked by the transformation of geography, towards an extensive global network, and by the intensification of collaborations between researchers. Brazil plays a decisive role in this context, with an accelerated growth of its scientific production accompanied by the expansion of domestic scientific collaborations (Grosseti et al. 2012).

Although still far from the growth pattern of China, Brazil acquires increasing relevance in the international scientific scenario, with production growth well above the world average. In the period between 1996 and 2008, Brazil was the third country in the world that presented the highest annual average growth in scientific production. The intensification of this growth trajectory occurred between 2002 and 2008, a period in which the growth of Brazilian production was about 110% (Grosseti et al. 2012).

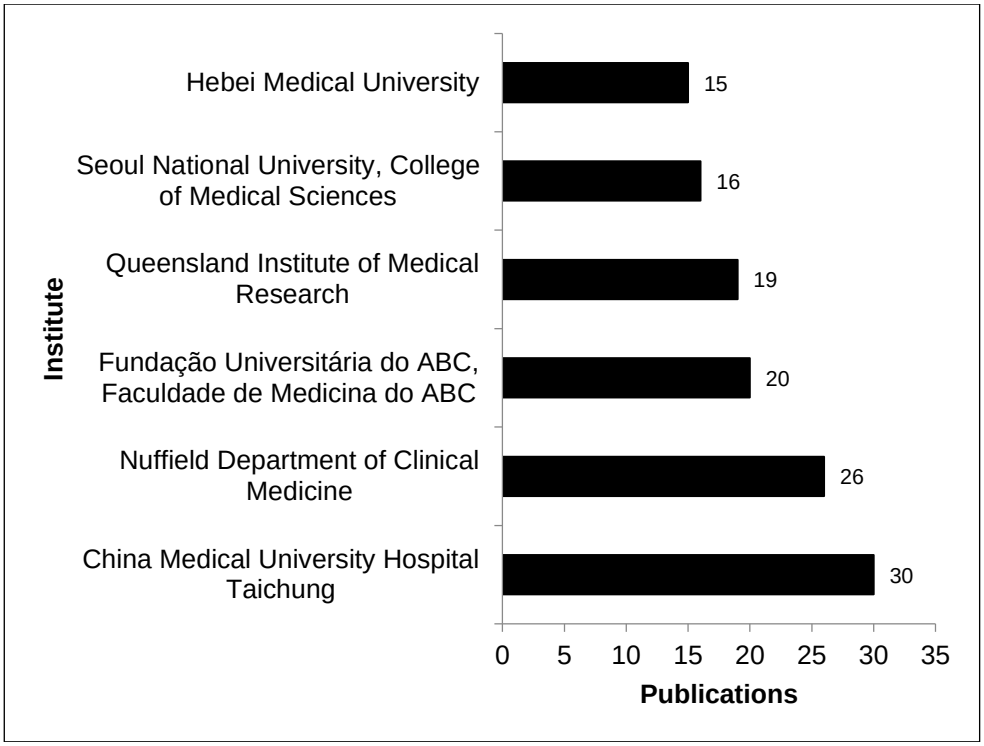

Figure 4. Main institutional affiliations of the most published authors about endometriosis and polymorphism between 1981 and 2013.

It was observed that the nine countries that published the most articles involving endometriosis and polymorphisms between 1981 and 2013 (Table 2) represent approximately 80% of all publications. It appears that the US appears with 77 articles, which is equivalent to 15% of the publications followed, in descending order from Japan, China, United Kingdom, Brazil, Italy, Taiwan, Australia and South Korea, with 56, 52, 48, 42, 41, 37, 32 and 32 articles, respectively.

Therefore, the USA was the country that most published. According to Pinto and Andrade (1999) the financial situation of research institutions in other parts of the world is more critical than the of the United States. Hence the difficulty of affiliated institutions in developing countries in promoting scientific activities. Another important aspect is the migration of scientists in developed countries, due to better financial advantages allied to the best infrastructure in relation to their country of origin (Currás and Barreiro 2008).

Brazil appears in fifth place. More than six million women are believed to be carriers of endometriosis here, a disorder considered a public health problem regardless of culture, race or ethnicity, as in some countries (Fourquet et al., 2010).

Table 2. Description of the nine countries that published 32 or more articles on endometriosis and polymorphism in the period 1981 to 2013.

Country	n	%
United States of America	77	12
Japan	56	8
China	52	8
United Kingdom	48	7
Brazil	42	6
Italy	41	6
Taiwan	37	6
Australia	32	5
South Corea	32	5
Total	417	80

Others	92	20
Grand Total	509	100

In relation to the language used in the writing of scientific articles, it was observed that English predominated with 468 published articles, making up approximately 91% of all publications, according to Figure 5. The large number of publications in the USA, once that the most published journals are American, justifies the predominance of the English language in the analyzed publications.

Initially, the languages of science were Latin and Italian, but gradually they gave place to other languages until the consolidation of English as the language of science (Meadows 1974). This fact has its origins in the dominating role that the British Empire has exercised in the last centuries as well as in the role of great economic and military power that the United States has assumed in the post-World War II (Crystal 2003). The growing presence of the English language as a fundamental component in global science is therefore unquestionable. Thus, having the mastery of a universal language is a requirement to be part of this universe, the central science (Filgueiras 2001).

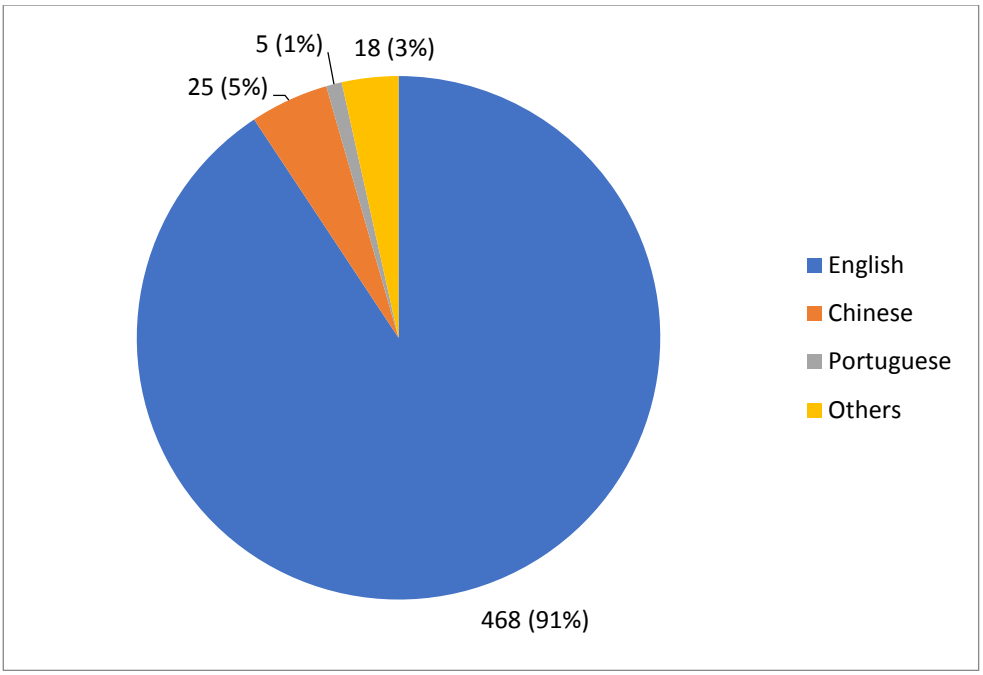

Figure 5. Most used languages in publications on endometriosis and polymorphism.

According to Table 3, the analysis of associations with polymorphisms in endometriosis revealed that 48 articles (10%) had an association with infertility, 34 articles (7.2%) with ovarian cancer and 4 articles (0.8%) with endometriomas.

Endometriosis is the cause of 10% of cases of infertility, a small but significant percentage. It is seen in up to 50% of the laparoscopies of patients undergoing infertility. The mechanisms that explain the pathophysiology are: tubal obstruction, pelvic adhesions and ovarian endometriomas that disrupt anatomical relationships and limit the access and mobility of the fimbriae to the ovary. Mild or moderate endometriosis is related to subfertility, with pregnancy rates of 17.7% in nine months (Marcoux et al. 1997; Velde et al. 2000; Gnoth et al. 2003). Endometriosis is still a clearer infertility factor in stages III and IV.

Another 75% of cases of infertility are caused by ovulation disorders, Fallopian tube obstruction and sperm abnormalities, and the remaining 15% are unknown (Tanahatoe et al. 2003).

The frequency of different histological subtypes of ovarian tumors varies according to age. While the germ cell tumors (GCT) predominate in the population below the age of 19 in adult women, epithelial origin predominates. Among malignant epithelial tumors occurring in women, approximately 10% corresponds to endometrioid carcinomas (Mink et al. 2002; Who et al. 2005). In children and adolescents, epithelial tumors correspond to 30% of ovarian tumors. Among the malignant, the proportion of borderline epithelial tumors in

young and infants ranges from 16% to 84% (You et al. 2005), predominating the serous subtype, followed by the messiness. However, malignant, or borderline endometrial tumors have not been described in this age group (Tsal et al. 2001).

Ovarian endometrioid tumors morphologically resemble uterine endometrioid neoplasms and, like other epithelial tumors, can be classified as benign, malignant, and borderline (Gilks 2006). In adult women, malignant tumors account for 10% to 25% of all ovarian tumors, with 3% to 18% of these carcinomas being of low malignant or borderline potential (Lee et al. 2003).

Endometrioid carcinoma occurs more frequently in women between the ages of 50 and 60 (Lee et al., 2003). These carcinomas most often present as a solid, bilateral tumor in 28% of cases. Clinically, it is usually asymptomatic, presenting as a pelvic mass, painful or not, with a serum elevation of CA 125 in 80% of the cases. Morphologically, they are characterized by the presence of atypical and confluent papillary gland structures, high mitotic activity and stromal invasion (Bell and Kurman 2000). Ovarian endometrioid carcinomas are associated with 15% to 20% of cases to endometrioid carcinomas in other regions and, in about 15% to 42%, occur concurrently with endometriosis (Wu et al., 2006). Nevertheless, most of these tumors are considered to originate from the ovary's own epithelial surface.

The Borderline Endometrioid Tumor is a rare neoplasm that affects patients between the ages of 22 and 77 years, although (Bell and Kurman, 2000) has reported in its series of cases a wider age range, from 24 to 85 years. Clinically, it presents as a palpable pelvic mass unilateral or with uterine bleeding. From the morphological point of view, it is characterized by the World Health Organization (WHO) as a tumor composed of atypical or cytologically malignant endometrioid glands, but without stromal invasion. More commonly it is solid idocístico, being the solid region characterized by the presence of glands with cytological atypia in the middle of the fibromatous stroma and the cystic region, by the hemorrhagic or mucous content. Mitotic activity is usually low, squamous metaplasia is common and areas with hemorrhage, infarction and necrosis may exist (Bell and Kurman 2000; L et al., 2003).

The prognosis of malignant endometrioid tumors is related to staging and histological grade, and the borderline tumor exhibits an excellent prognosis when compared to endometrioid carcinoma (Lee et al. 2003). Ovulation rates in women with ipsilateral endometrioma are lower compared to contralateral ovaries without endometrioma (22 × 50%) (Benaglia et al., 2009). It remains controversial whether resection of asymptomatic endometrioma improves fertility. In the literature, several studies have shown that resection of endometrioma generates a loss of follicles adjacent to the cyst wall and, therefore, may reduce oocyte uptake by compromising fertility (Ragni 2005).

This possibility has been supported by several studies that compared the ovary operated with the contralateral ovary during ovarian hyperstimulation *in vitro* fertilization and observed that the ovary operated produces fewer dominant follicles, oocytes, and high-quality embryos than intact ovaries (Ragni 2005). Busacca et al. (2006), in a case series study, reported that three of 126 patients with a mean age of 30.4 years developed ovarian failure immediately after the excision of bilateral endometriomas. Tsoumpou et al. (2009) performed a meta-analysis that included five studies comparing the pregnancy rate in women with endometriomas who underwent surgery with those who did not receive any treatment and there was no significant difference.

Table 3. Associations with polymorphisms in endometriosis between 1981 and 2013.

Associations	**n**	**%**
Infertility	48	10
Ovarian Cancer	34	7,2
Endometrioma	4	0,8
Total	**86**	**18**
Others	385	82
Grand total	**471**	**100**

When articles referring to GWAS and endometriosis were analyzed, 18 articles were found between the years 2010 to 2017, not specifically of genetic polymorphism but of candidate genes. In relation to the studied genes, 12 articles (2.4%) mentioned GSTM 1, 5 articles (1%) PROGINS, 4 articles (0,8%) GSTT1 and CYP1A1 (Table 4).

Among the most known GSTs enzymes are GSTT1 and GSTM1 (Rossit and Froes 2000). Homozygous for the null GSTM1 allele are considered a risk group, especially if exposed to high levels of carcinogens and chemical compounds, due to the enzymatic defect in their detoxification system (Baranova et al. 1997).

Table 4. Genes studied in polymorphisms in endometriosis between 1981 and 2013.

Genes	n	%
GSTM1	12	2,4
PROGINS	5	1
GSTT 1	4	0,8
CYP1A1	4	0,8
Total	**25**	**5**
Others	446	95
Grand total	**471**	**100**

In relation to CYPs enzymes, one of the most extensively studied is CYP1A1. A restriction polymorphism MspI (CYP1A1m1) in the 3 'non-coding region of the gene, resulting from the transition from a thymine to cytosine (T®C), appears to promote increased expression (Arvanitis et al. 2001). The availability of information on CYP1A1m1, GSTM1 and GSTT1 polymorphisms in the Brazilian population is scarce.

Other candidate genes for association with risk for endometriosis that also deserve investigation include genes encoding androgen hormone receptors, estrogen and progesterone receptors (Kitawaki et al., 2002). The biological actions of progesterone are mediated by two isoforms of its receptor, respectively A and B (Li X and O'Malley, 2003). In the endometrium both progesterone receptor subtypes are expressed, and their concentration varies according to the phase of the menstrual cycle. If there is a predominance of isoform B (Mulac-Jericevic et al., 2000), there is no adequate action of progesterone, thus speculating that perhaps this alteration is related to the genesis of endometriosis.

Recently, several progesterone receptor polymorphisms have been described. Among them, the PROGINS polymorphism (Donaldson et al. 2002) stands out. It has been studied in association with estrogen-dependent conditions and all data indicate that a mutation in the progesterone receptor gene contributes to the development of diseases in hormone-dependent tissues, including endometriosis (Cramer et al. 2003).

CONCLUSION

It was observed that there was a tendency of increase in the number of publications over the years with a slight decline in the year of 2004 and peak in the year of 2013 being that the works were mostly original articles. It was verified that the most published authors are from developing countries, as well as the magazines and the institutions, justifying the predominance of the English language in the writing of the same ones. The average impact factor of the reviewed journals was 3,481. Developing countries, among them Brazil, have less contribution in studies of endometriosis and polymorphisms, which confirms the need for Scientometric studies to arouse the interest of governments and institutions that promote research in these countries, in order to have greater investment. Different associations were studied, with a greater number of published works with infertility, ovarian cancer and endometrioma. In the various types of studies performed, there is a predominance of GSTM1 gene. Therefore, there is a multidisciplinary interest in the study of endometriosis and that despite the great advance in its research, there is still much to study to improve the diagnosis, treatment and, consequently, the patients' quality of life.

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