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PUBLICATION TRENDS IN RADIOTHERAPY AND FEMALE INFERTILITY: A SCIENTOMETRIC STUDY

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ABSTRACT

A common cancer treatment, radiotherapy, has deleterious effects on reproductive health, especially by decreasing the capacity for conception. The objective of this study was to analyze the research trend associated with radiotherapy and female infertility until June 2023. SCOPUS database was utilized to obtain pertinent scientometric information (annual publications, affiliations, journals, countries, document types, and research areas) for various radiotherapy subgenres and female infertility. A total of 910 articles were published related to radiotherapy and female infertility, with the United States of America (USA) leading the way in research output in this field. Over the years, radiotherapy and female infertility research have shown positive progress. In-depth analysis revealed that publications (n) related to radiotherapy and female infertility research mainly focused on its impact on ovarian tissue (n = 574) and fertility preservation techniques (n = 390). These scientometric results highlight a limited research focus on the field of radiotherapy and its impact on female reproductive hormones and female accessory reproductive organs. Furthermore, a significant lack of research has been noted in omics and female reproductive organs linked to radiotherapy. Extensive scientific research is necessary to further unravel the impact of radiotherapy on female infertility at the molecular level.

Keywords: Radiation therapy, female fertility, fertility preservation, reproductive hormones, omics

INTRODUCTION

According to the World Health Organization (WHO), infertility is defined as the condition where a couple fails to achieve a pregnancy after having regular unprotected sexual intercourse for 12 months or more. Infertility affects between 48 million couples and 186 million people worldwide (**WHO, 2024**). Infertility issues are prevalent, with 10% of females experiencing such challenges, and the probability of infertility increases with age (**Cleveland Clinic, 2020**). Another WHO study reported that in 37% of infertile couples, female factor infertility was the cause (**WHO, 1992**). Infertility in females is either primary, which means when a female never conceived, or secondary, where a female had successfully conceived once but could not conceive in the subsequent unprotected coitus (**Bhattacharya *et al.*, 2010**). Causes of female infertility include genetic anomalies, hormonal imbalances, endocrine disruptions, and exposure to environmental factors (**Tarin *et al.*, 2015**). Additionally, infertile females have an increased risk of developing gynecological malignancies (**Lerner-Geva *et al.*, 2012**).

Common causes of female infertility, as identified by the WHO in 1992, include ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (12%), tubal blockage (11%), hyperprolactinemia (7%), and other tubal and uterine abnormalities (11%) (**WHO, 1992**). Furthermore, polycystic ovary syndrome (PCOS) accounts for 46% of female infertility cases (**Deshpande and Gupta, 2019**). In addition, the amount of radiation the ovaries receive during therapy determines whether or not a woman will become infertile, particularly when the radiation is targeted near the abdomen or pelvis (**American Cancer Society, 2020**). Furthermore, high-energy rays block the ability of cancerous cells to divide and proliferate. Cells that grow uncontrollably and acquire metastatic properties become cancerous. In the United States of America (USA), about 948,000 new cancer cases are reported by females and approximately 287,740 is the estimated number of deaths (**Siegal et al., 2023**). For the year 2024 new cancer cases and cancer deaths have been projected at 2,001,140 and 611,720, respectively in the USA (**Siegal et al., 2024**).

Different cancer treatments, including biomarker testing, chemotherapy, hormone therapy, hyperthermia, immunotherapy, photodynamic therapy, stem cell transplant, surgery, targeted therapy, and radiotherapy, have varying impacts on fertility (**National Cancer Institute, 2023**). In terms of new cancer cases, the most common cases in 2020 included breast (2.26 million cases), lung (2.21 million cases), colon and rectum (1.93 million cases), prostate (1.41 million cases), non-melanoma skin (1.20 million cases) and stomach (1.09 million cases) cancers (**WHO, 2020**). In 2022, 20 million new instances and 9.7 million deaths from the disease were reported by the WHO (**WHO, 2024**). Radiotherapy, involving high-energy ionizing radiation to kill or inhibit cancer cell growth, can cause ovarian failure and uterine damage, affecting foetal development (**Bath *et al.*, 1999,2003; Hu *et al.*, 2016**). Radiation therapy is administered to over 50% of cancer patients at least once during the course of their illness (**Baskar *et al.*, 2012**). It is reported that ionizing radiation of about 25-30 Gy has the potential to cause infertility in almost all females above the age of 40 years (**Marci *et al.*, 2018**). During childhood, women who have received flank radiotherapy pose an increased risk of having a pregnancy complicated by hypertension, malposition of the foetus, premature labour along with a risk of delivering a low-weight baby and even premature birth (**Green *et al.*, 2002**). Radiotherapy is becoming a very reliable treatment option for cancer patients across the globe with the growing number of cancer cases, yet the effect of radiotherapy on fertility has become a major concern among female cancer patients. Hence, cancer patients opt for various fertility preservation techniques post-radiotherapy.

Bibliometrics and scientometrics research focus on measuring and analyzing the scholarly literature. A bibliometric analysis of infertility literature reported 6,424 publications from 2011 to 2015, with the USA, England, Netherlands, China, and Germany leading in publications (**Makkizadeh and Sa'adat, 2017**). Another quantitative bibliometric study analyzed a total of 62,550 scientific publications on global radiation therapy research over the period of 2001 to 2015. The majority of

the articles – 60,494 (or 96.70%) were written in English, but there were also 20 other languages, with the three most common being French (1,193, i.e., 1.90%), German (598, i.e., 0.96%), and Spanish (76, i.e., 0.12%) (**Agarwal *et al.*, 2018**). While another scientometric analysis found 104 studies investigating the impact of non-ionizing electromagnetic field exposure on fertility considering a 26-year period, from 1996 to 2016. Journals like Bioelectromagnetics (8 papers, 7.50%), Reproductive Toxicology (6 papers, 5.70%), Fertility and Sterility (4 papers, 3.80%), and Electromagnetic Biology and Medicine (11 papers, 10.40%) all saw larger numbers of studies published (**Bernabo *et al.*, 2017**).

Thus, the rising incidence of cancer and the widespread use of radiotherapy underscore the urgent need to understand its impact on female fertility. Despite the effectiveness of radiotherapy in treating cancer, its potential to cause infertility raises significant concern. This study aims to address gaps in current research, offering a comprehensive analysis of publications on radiation and female infertility up to June 2023. By identifying research gaps, this study seeks to aid future investigations and improve fertility preservation strategies for female cancer patients.

MATERIAL AND METHODS

Ethics statement

Since this is a scientometric analysis, the study did not require the participation of human or animal subjects. It was conducted using data retrieved from the SCOPUS database, and as such, it is exempt from review by the Institutional Review Board.

Data source

The present scientometric analysis was conducted using the SCOPUS database. One of the most inclusive, comprehensive and multidisciplinary bibliographic databases, Elsevier's SCOPUS covers 94 million documents, 2.4 billion cited documents with the oldest record dating back to 1788 and 19.60 million author profiles (**Elsevier Scopus, 2024**). SCOPUS metrics, which is the number of publications per year, author and their affiliations, journals, countries, types of documents, subject areas and the number of citations on radiotherapy and female fertility, were obtained using the SCOPUS operational functions, and those data were analyzed.

Data retrieval strategy

A SCOPUS literature search was conducted but it was limited to human studies that were published until June 2023. Relevant keywords were selected for each step, and in some cases, an 'asterisk' (*) was used just after the keyword so that the search could include all the variants of that particular word. Functions and Boolean operators were used, e.g., "TITLE-ABSTRACT", "TITLE-ABSTRACT-KEYWORDS", "AND", "OR", "NOT" and "AND NOT" to obtain relevant scientific literature. The search was conducted in July 2023 and was done in 6 steps using relevant keywords as illustrated in **Figure 1**. After the files were extracted, the relevance of all the articles was examined by the researchers, individually, by screening the title and abstract of the articles extracted in each step. The scientific literature that consisted of animal studies, male studies and those that are irrelevant to the topic were excluded. **Table 1** contains the list of keywords used for the SCOPUS search.

Scientometric analysis

The extracted scientometric data were saved as comma-separated value files (CSV) and were then, for in-depth analysis, the files were converted to Microsoft Excel files. Based on the scientometric analysis of radiotherapy and female infertility research worldwide, geographic mapping was obtained using Microsoft Excel. VOS software generated a network map of international collaborations in radiotherapy and female infertility research.

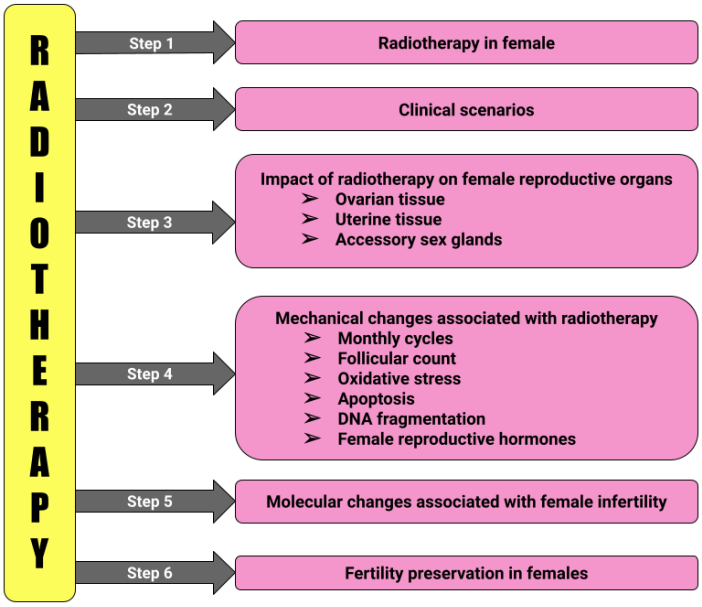


Figure 1 The framework of scientometric analysis. Step 1 analyzed the effect of radiotherapy in females. Step 2 analyzed the impact of radiotherapy in females and associated clinical scenarios. Step 3 focused on the effect of radiotherapy on female reproductive organs. Step 4 analyzed the aspects of monthly cycles, follicular counts, oxidative stress, apoptosis, DNA fragmentation and female reproductive hormones. Step 5 and finally Step 6 analyzed respectively the effects of radiotherapy on molecular changes associated with female infertility and preservation of fertility in females.

Table 1 Keywords used to retrieve documents from the SCOPUS database.

STEP	CONTENT	KEYWORD STRING
1	Radiotherapy and female reproductive research	TITLE-ABS ("fertility") AND TITLE-ABS ("radiotherap*" OR "radiation therap*" OR "radiation treat*") AND TITLE-ABS-KEY ("human" OR "woman" OR "women" OR "female*") thereafter referred to as STRING (A)
2	Radiotherapy in women and clinical scenarios	(A) AND TITLE-ABS-KEY ("polycystic ovary syndrome*" OR "PCOS" OR "polycystic ovarian disease*" OR "PCOD" OR "ovarian cancer*" OR "ovar* cancer" OR "endometriosis" OR "cervical cancer*" OR "cervi* cancer" OR "vaginal cancer*" OR "vagina* cancer" OR "uterine cancer*" OR "vulvar cancer*" OR "vulva* cancer" OR "preeclampsia" OR "pre-eclampsia" OR "recur* pregnancy loss*" OR "recurrent miscarriage" OR "consecutive pregnancy loss" OR "consecutive miscarriage")
3	Impact of radiotherapy on female reproductive organs	
	3a Ovarian tissue	(A) AND TITLE-ABS-KEY ("ovar* tissue*" OR "ovar* cell" OR "ovar*")
	3b Uterine tissue	(A) AND TITLE-ABS-KEY ("uter* tissue" OR "uter* cell" OR "uter*")
	3c Accessory sex glands	(A) AND TITLE-ABS-KEY (A) AND TITLE-ABS-KEY ("Bartholin's gland*" OR "Skene's gland*" OR "lesser vestibular gland*" OR "mammary gland*" OR "mammary*" OR "breast*")
4	Mechanistic studies on impact of radiotherapy on female fertility	
	4a Monthly cycles	(A) AND TITLE-ABS-KEY ("menstrua* cycle*" OR "menses")
	4b Oocyte and follicular count	(A) AND TITLE-ABS-KEY ("oocyte count" OR "oocyte number" OR "egg count" OR "egg number" OR "follic* count" OR "follic* number")
	4c Oxidative stress	(A) AND TITLE-ABS-KEY ("ovar* follicle" OR "follicular fluid" OR "fallopian tube" OR "peritoneal cavity") AND TITLE-ABS-KEY ("reactive oxygen species" OR "ROS" OR "oxidative damage" OR "oxidative stress")
	4d Apoptosis	(A) AND TITLE-ABS ("oocyte" OR "granulosa cell*" OR "Graafian follicle*" OR "primary follicle*" OR "primordial follicle*" OR "secondary follicle*" OR "follic*") AND TITLE-ABS-KEY ("apoptosis" OR "programmed cell death" OR "caspase")
	4e Oocyte and follicular DNA fragmentation	(A) AND TITLE-ABS-KEY ("oocyte" OR "egg" OR "follic*) AND TITLE-ABS-KEY ("DNA damage" OR "DNA fragment*")
	4f Female reproductive hormones	(A) AND TITLE-ABS-KEY ("progesterone*" OR "estrogen*" OR "oestrogen*" OR "luteinizing hormone" OR "follicle stimulating hormone" OR "LH" OR "FSH")
5	Radiotherapy and molecular changes associated with female infertility	
	Genomics, proteomics, metabolomics	(A) AND TITLE-ABS-KEY ("genomic*" OR "transcriptomic*" OR "proteomic*" OR "metabolomic*" OR "microRNA*" OR "miRNA*" OR "epigenetic*")

6	Radiotherapy and fertility preservation in women	(A) AND TITLE-ABS-KEY (“woman” OR “women” OR “female*” OR “ovar*” OR “uter*” OR “follic* OR “cervi*” OR “vagina*”) AND TITLE-ABS-KEY (“cryopreservation” OR “cryoconservation” OR “retransplantation” OR “ovarian transposition” OR “embryo bank*” OR “oocyte bank*” OR “surroga*”)

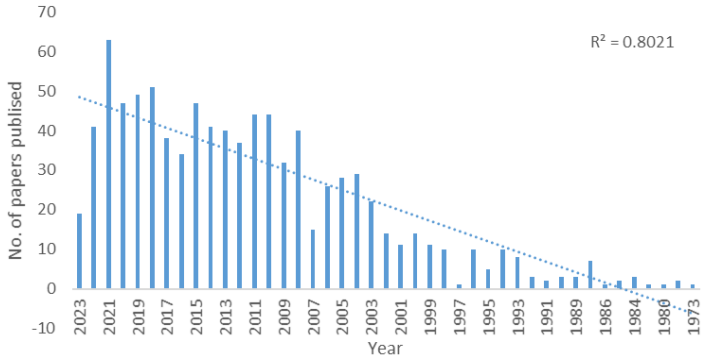
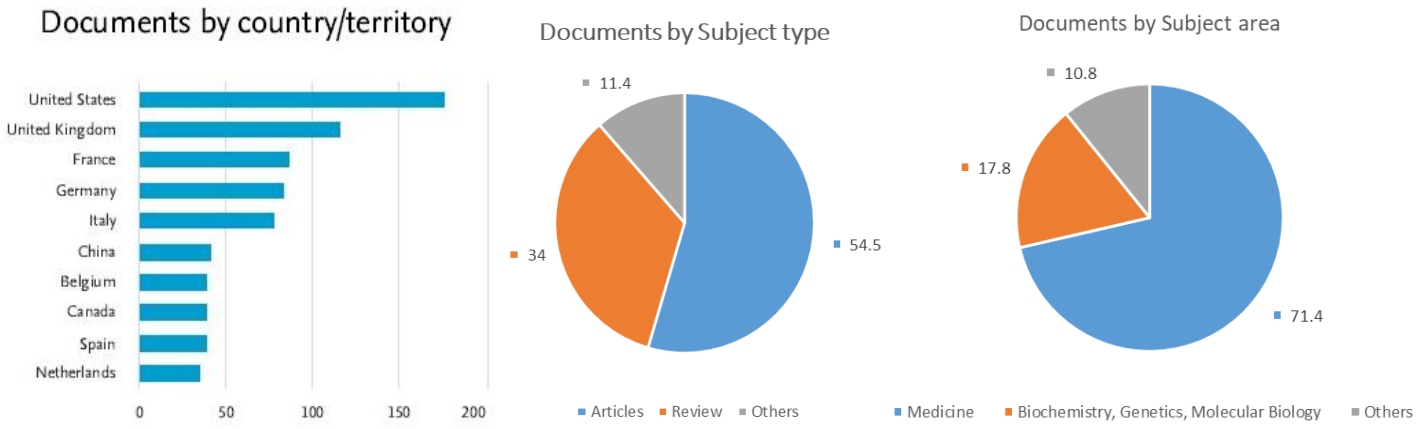


Figure 2 Number of publications per year related to the impact of radiotherapy research on female fertility. The trendline signifies an overall steady increase in research focus in this field.



A) **B)** **C)**

Figure 3 Research trends based on the A) Country/territory, B) type of documents and C) documents by subject area published related to radiotherapy research in female infertility.

RESULTS

Trends of publications in female infertility and radiotherapy research

The overall research trend shows that 910 articles have been published in the field of radiotherapy and female fertility until June 2023 which is approximately 21 articles per year on average ($R^2 = 0.8021$). **Figure 2** shows that the highest number of papers were published in the year 2021, followed by 2018 and 2019. The USA produced the highest number of papers in this field whereas the UK and France were in the second and third positions, respectively. About 71.40% of the papers (n = 860) were in the field of Medicine whereas 17.80% (n = 214) were Biochemistry, Genetics and Molecular Biology. Almost 54.50% (n = 496) were original articles, 34% (n = 309) were reviews, and 11.40% (n = 105) were book chapters followed by the rest of the categories such as conference papers, short surveys, books, editorials and notes (**Figure 3**). A map of country network visualization is presented in **Figure 4** using VOS software along with a geo map prepared using Microsoft Excel as shown in **Figure 5**.

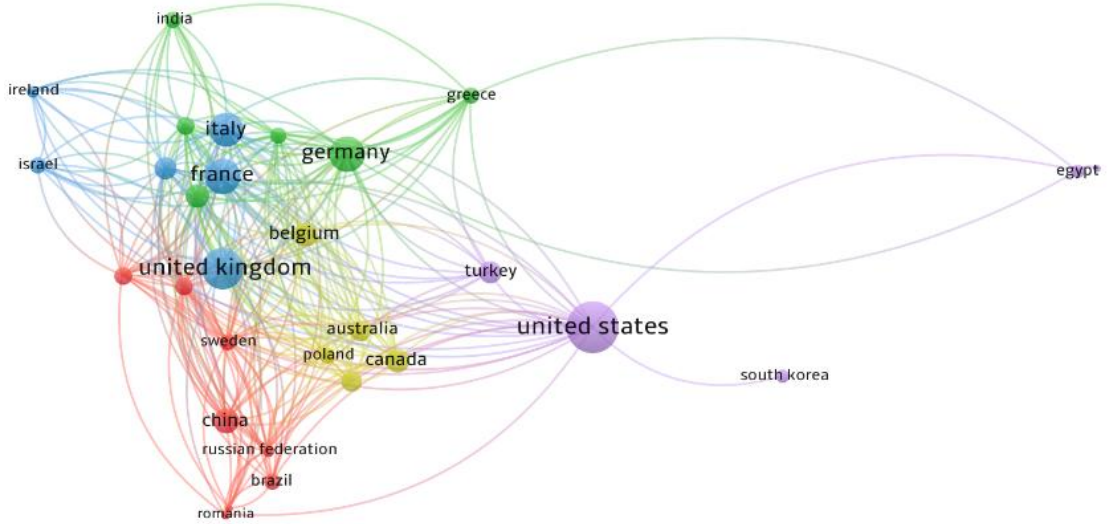


Figure 4 Network map showing the international collaboration among various countries based on publications in the field of radiotherapy research and female fertility. VOS Viewer version 1.6.19.

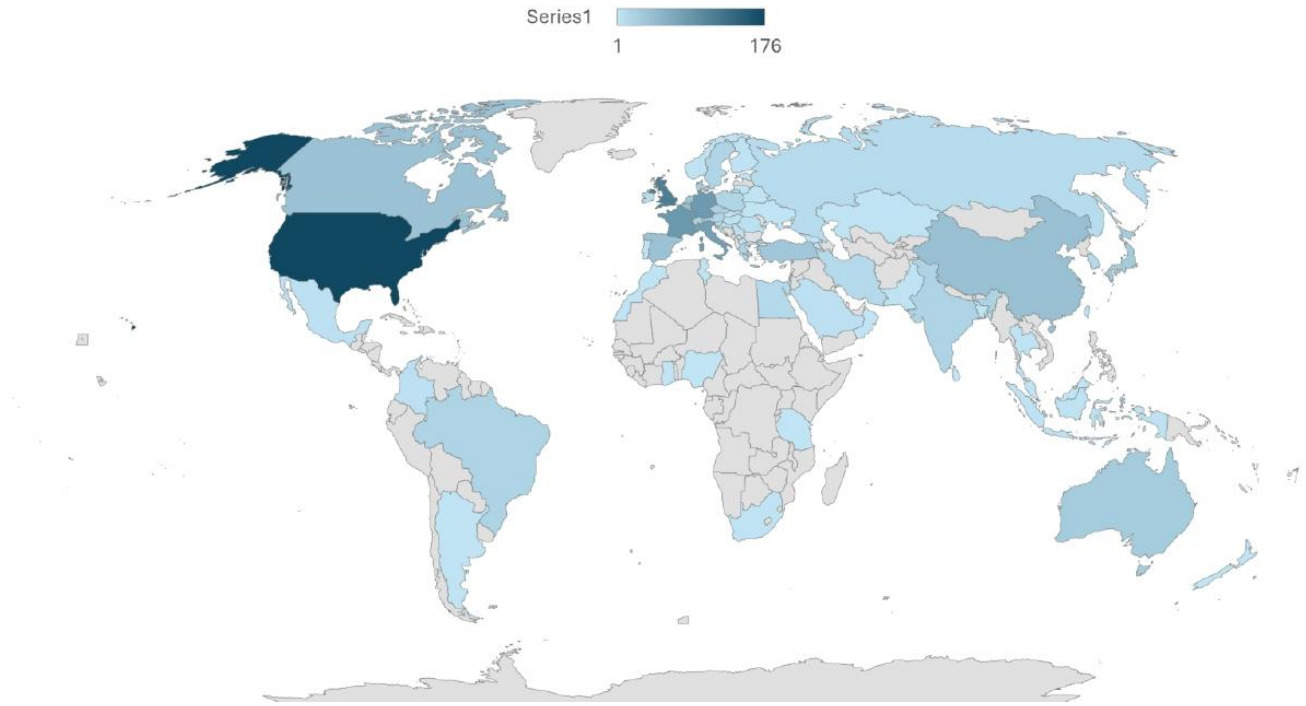
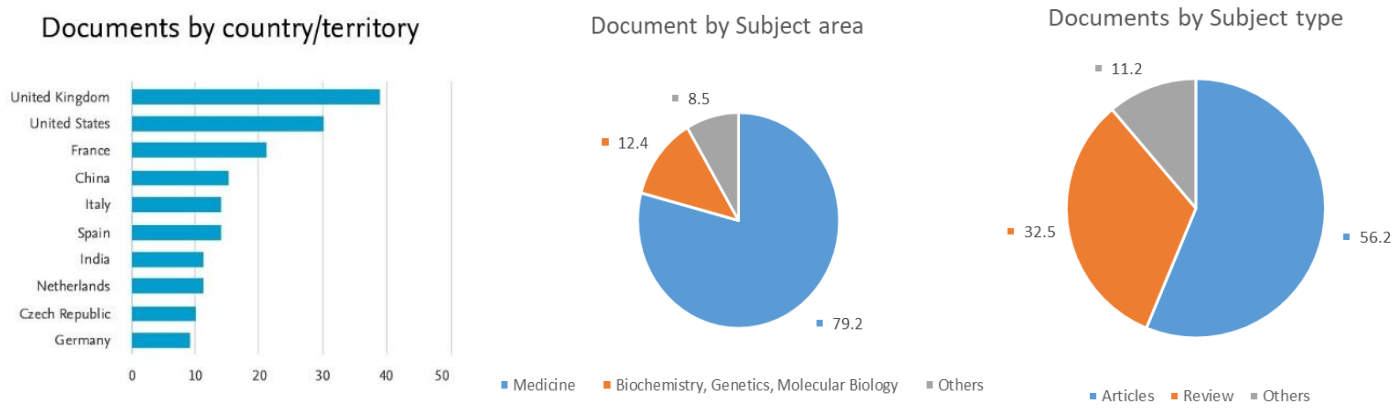


Figure 5 Geomap showing the distribution of publications from countries contributing to the field of research concerning radiotherapy and its impact on female fertility.



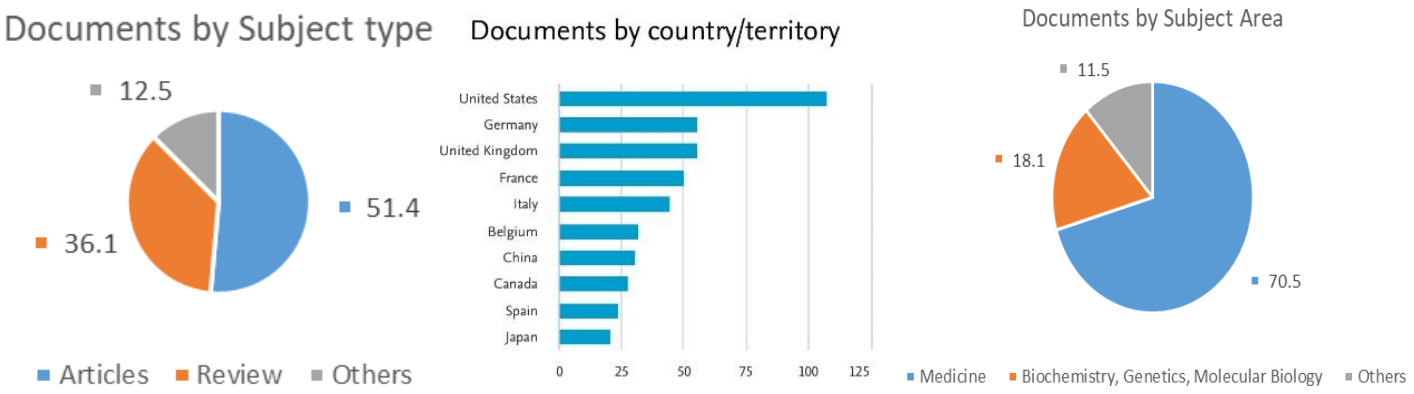
A) **B)** **C)**

Figure 6 Research trends based on the A) country/territory, B) type of documents, and C) documents by subject type related to radiotherapy and female reproductive organs.

An in-depth analysis showed that approximately 70% (n = 169, 169/242) of articles discussed the use of radiotherapy in different clinical scenarios associated with female reproductive organs. Among these, almost 56.20% (n = 95) and 32.50% (n = 55) publications were original and review articles, respectively. Out of these, approximately 79.20% (n = 160) were in the area of Medicine, and 12.40% (n = 25) were in the area of Biochemistry, Genetics and Molecular Biology. **Figure 6A** shows that the top three countries publishing in this area are the United Kingdom (UK, n = 39), USA (n = 30) and France (n = 21). **Figure 6B** shows the subject area of the documents related to radiotherapy research in female infertility whereas **Figure 6C** represents the subject type related to radiotherapy and female reproductive organs.

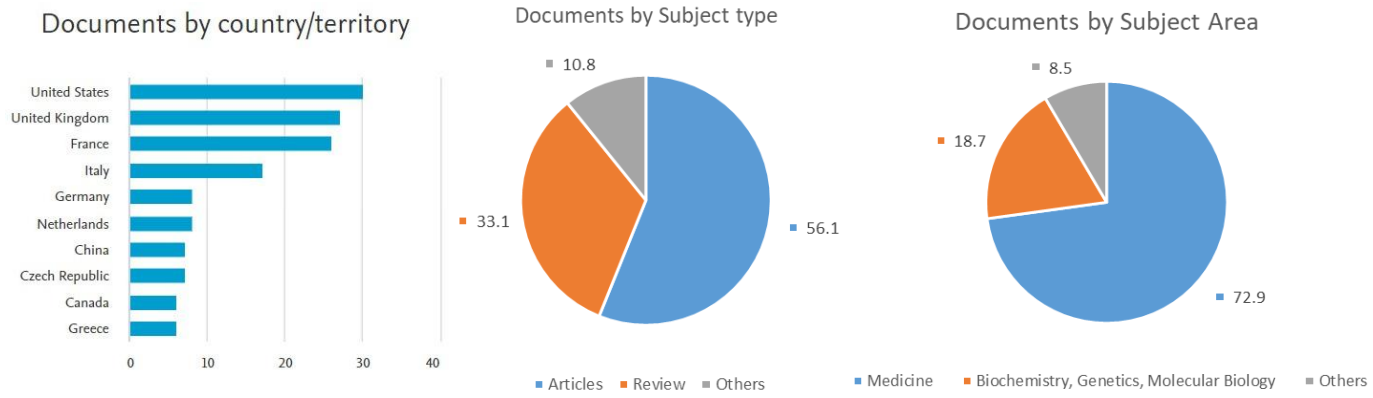
Trends of publications on the impact of radiotherapy on female reproductive organs

Research trend analysis revealed that 574 articles were published until June 2023 on the impact of radiotherapy and ovarian tissue. The highest number of papers (n = 45) were published in the year 2021 followed by the year 2022 (n = 30). Among these, approximately 51.40% (n = 295) and 36.10% (n = 207) publications were original and review articles, respectively. Out of these, just over 70.50% (n = 541) were in the area of Medicine, and 18.10% (n = 142) were in the area of Biochemistry, Genetics and Molecular Biology **(Figure 7)**. The highest numbers of papers were published by the USA followed by Germany and the UK. The top three countries publishing in this area were the USA (n = 107), Germany and the UK (n = 55 each). Research works on uterine tissues showed that only 157 articles were published until June 2023. Out of these 15 articles were published in 2021, which was the highest, followed by 14 articles in 2018 and 11 articles in 2020. Approximately 56% (n = 88) were original articles followed by 33% (n = 52) review articles. Among them, almost 72.90% (n = 148) were in the area of Medicine, followed by 18.70% (n = 38) in the area of Biochemistry, Genetics and Molecular Biology. Top 3 countries publishing in this specific area are the USA, UK and France, respectively **(Figure 8)**. Finally, publications on female accessory reproductive organs showed only 113 articles whereas 2015 showed the highest number of articles published in this area. Over 69% (n = 109) of articles were in the area of Medicine, followed by 22% (n = 35) in Biochemistry, Genetics and Molecular Biology, and 3% (n = 5) in Nursing. Of these, over 51% (n = 58) were original articles, 37% (n = 42) were review articles, and 6% (n = 7) were book chapters **(Figure 9)**



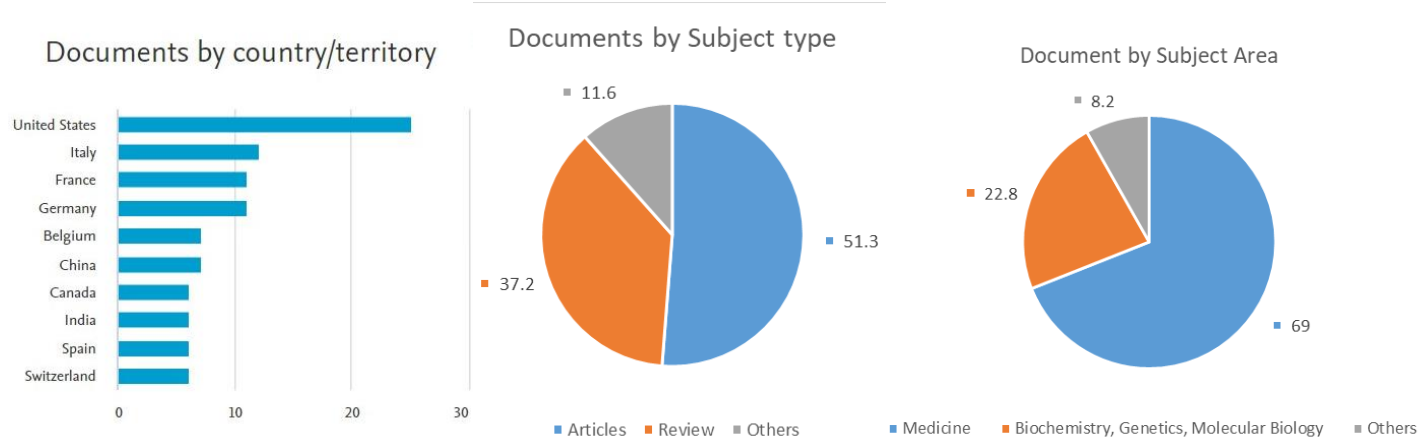
A) **B)** **C)**

Figure 7 Research trends based on the A) type of documents, B) country/territory, and C) subject area related to radiotherapy and ovarian tissues.



A) **B)** **C)**

Figure 8 Research trends based on the A) country/territory, B) type of documents and C) subject area related to radiotherapy and uterine tissues.



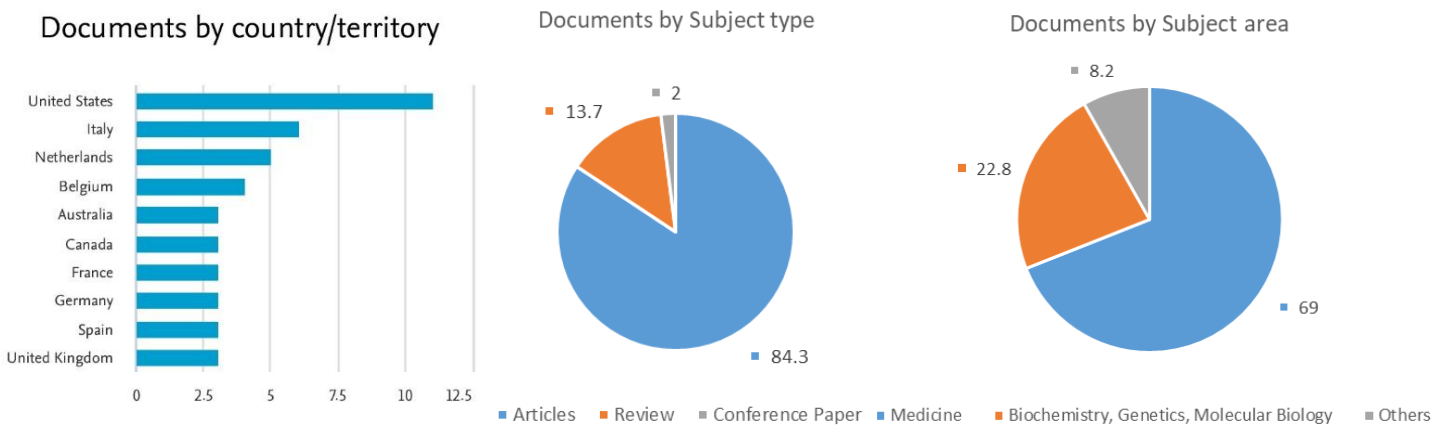
A) **B)** **C)**

Figure 9 Research trends based on the A) country/territory, B) type of documents and C) subject area related to radiotherapy and accessory sex glands

Trends of publications on mechanistic studies on the impact of radiotherapy on female fertility

In the present scientometric study, almost 73% (n = 51, 51/70) of papers were published in the area of monthly cycles or menstrual cycles most of which are original articles (n = 43, 84.30%) followed by review articles (n = 7, 13.70%) and a conference paper. The majority of the publications were in the area of Medicine (68.10%) followed by Biochemistry (22.20%) and Neuroscience (2.80%). The top 3 countries publishing in this area are the USA, Italy and Netherlands (**Figure 10**).

Interestingly, only nine (n = 9) studies focused on oocytes and follicular count and 1 article each related to oxidative stress, and oocyte and follicular DNA fragmentation. Papers related to apoptosis were only five (n = 5). However, the present study revealed that more papers (n = 83) were published in the field of female reproductive hormones, where original articles were almost 63%, followed by review articles (30%) and the rest were book chapters, conference papers and short surveys. Most of the papers were in Medicine (73.60%) followed by Biochemistry (22.70%). The top 3 countries publishing in this field are Germany, USA, and UK.



A) **B)** **C)**

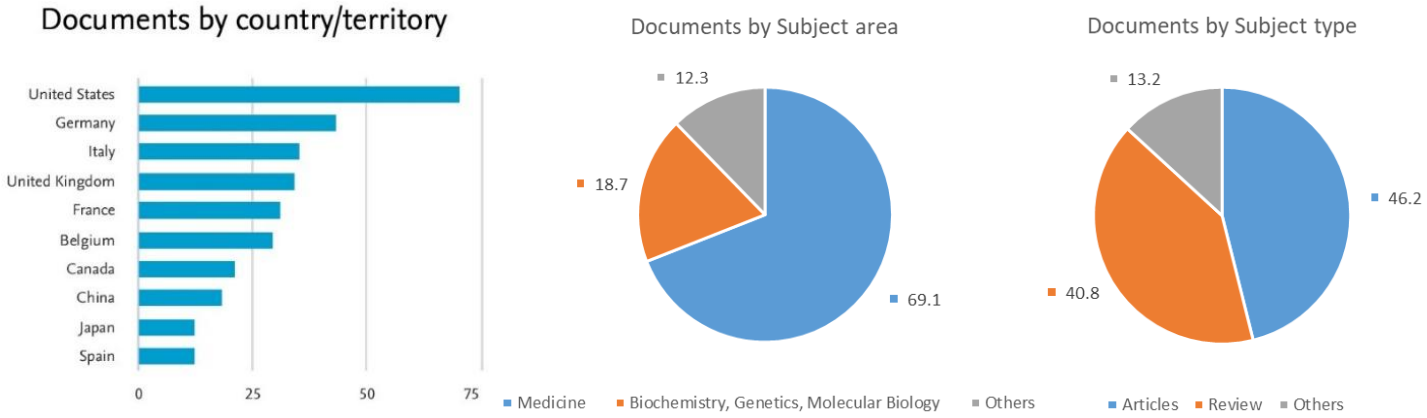
Figure 10 Research trends related to radiotherapy and menstrual cycle based on A) country/territory B) subject area and C) subject type.

Trends of publications on radiotherapy and molecular changes associated with female fertility

The impact of radiotherapy on molecular alterations in female reproductive organs was the subject of the penultimate step of the scientometric analysis of publication trends. Only two articles (n = 2) were published in this field until June 2023 both being review articles in the area of Medicine.

Trends of publications on radiotherapy and fertility preservation in females

The topic of radiation and female fertility preservation has been the subject of 390 (n = 390, 390/474 i.e., 82.27%) publications. These studies have provided a comprehensive understanding of the impact that radiation can have on the preservation of female fertility. Publications in this area spiked in the year 2021 followed by 2022. The majority of the articles belonged to the area of Medicine (n = 363, 69.10%), followed by Biochemistry, Genetics, and Molecular Biology (n = 99, 18.70%). Among these, over 46.20% (n = 180) were original articles, 40.80% (n = 159) were review articles, 7.70% (n = 30) were book chapters, and the rest belonged to other categories. **Figure 11** shows that USA (n = 33, 19.52%) was the leading country that published scientific literature in this field (n = 70), followed by Germany (n = 43) and Italy (n = 35). Country network visualization made using VOS software is depicted in **Figure 12**.



A) **B)** **C)**

Figure 11 Research trends based on the A) country/territory, (B) type of documents by subject area and C) subject type related to radiotherapy research in female fertility preservation.

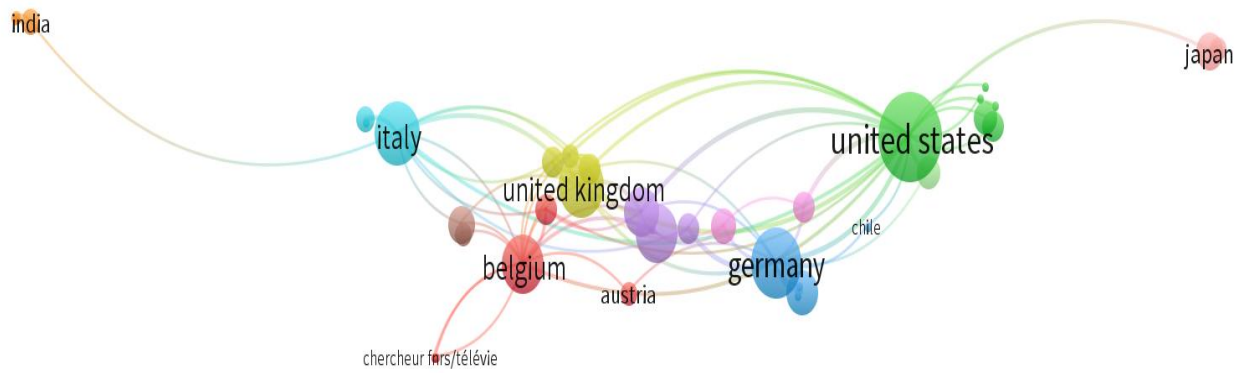


Figure 12 Network map showing the international collaboration among various countries based on publications in the field of radiotherapy and female fertility preservation. VOS Viewer version 1.6.19

DISCUSSION

Radiotherapy plays an important role in treating different cancers, yet they have long-term toxic effects on the female gonads including ovarian insufficiency, pubertal arrest and subsequent infertility (**Marci *et al.*, 2018**). Understanding these adverse effects is essential given the growing trend of radiotherapy as a preferred cancer treatment option. This study employed a scientometric technique to examine publication trends related to female infertility and radiotherapy up until June 2023. The scientometric analysis provides insights into how scholarly publications influence the development of specific research fields (**Roldan-Valadez *et al.*, 2019**). SCOPUS, one of the largest databases of curated abstracts and citations, was utilized for this research (**Baas *et al.*, 2020**). SCOPUS encompasses a wide range of fields, including physical sciences, health sciences, social sciences, and life sciences (**UNC, 2024**). Of late, several researchers have also employed this approach in their scientometric analyses, examining the distribution of publications according to their area of interest (**Martynov *et al.*, 2020; Jain *et al.*, 2022, Roychoudhury *et al.*, 2022; Wang *et al.*, 2023**).

Cancer remains a leading cause of death among women globally, with significant burdens anticipated in the coming decades. An estimated 20 million new cancer cases and 10 million cancer-related deaths occur worldwide annually, with the cancer burden expected to rise by nearly 60% by 2040, further straining healthcare systems and communities (**PAHO, 2023**). The most popular non-surgical treatment option for cancer happens to be radiotherapy (**Mohan *et al.*, 2019**). Radiotherapy is a cost-effective, non-surgical treatment, comprising about 5% of overall cancer treatment costs (**Ringborg *et al.*, 2003**). However, it is associated with fertility impairment, primarily through the disruption of the hypothalamic-pituitary axis in women, leading to ovarian failure and making the uterus unsuitable for foetal growth (**Wo and Vishwanathan, 2009**). Research in this area should be given greater attention due to the growing trend of radiotherapy being the preferred treatment option for cancer patients who also have increased infertility issues (**Roychoudhury *et al.*, 2022**). The scientometric analysis revealed an increase in publications on the effects of radiotherapy on female fertility, from a single publication in 1973 to 63 articles in 2021. This increase suggests a growing interest in the scientific community to explore the impact of radiotherapy on female fertility. Original articles comprised approximately 55% of all publications, indicating robust research activity in this field. Notably, 71.40% of these publications were in the field of Medicine, emphasizing the clinical focus on developing treatments to mitigate the effects of radiation on fertility (**Falls *et al.*, 2018; Ahmad *et al.*, 2019**). Previous studies also support our proposition, showing that research is advancing towards reducing the harmful effects of radiotherapy on fertility (**Das *et al.*, 2011; Barazzoul *et al.*, 2020**). Several strategies have been proposed to reduce the negative effects of radiation, including proton radiation, intensity-modulated radiation therapy, gonadal shielding, and ovarian transposition (**Wo and Viswanathan, 2009; Marci, 2018**). Yet more investigations are vital for evaluating the effect of such techniques on female reproductive organs since these may benefit young cancer survivors. In our analysis, USA emerged as a leading country in radiotherapy-related female infertility research, with the University of Texas and the University of Edinburgh being the top two institutions in this field. Additionally, the study noted an increasing trend in research from UK and France.

Cancer is a prominent cause of death among women globally both in high and middle-income countries (**Torre *et al.*, 2017**). According to a WHO report, 670000 cases of female deaths were reported due to breast cancer alone in the year 2022 (**WHO, 2022**). Radiotherapy has gonadotoxic effects in women (**Marci, 2018**) which concerns researchers around the globe (**Jeruss and Woodruff, 2009**). It is particularly evident from the findings of the present scientometric analysis as the number of publications has substantially increased in the area of radiotherapy and female clinical scenarios – the highest being in the year 2022. This scientometric analysis revealed a considerable number of publications (n = 95) in the area of radiotherapy and its impact on the clinical scenarios linked with female reproductive organs. Radiotherapy has been found to cause infertility and early menopause in women (**American Cancer Society, 2024**). Therefore, investigations are necessary to comprehend the functionality and reproductive potential of females with cancer receiving radiotherapy. This was in concordance with the increase in the publication trends of radiotherapy and female reproductive research in UK, USA and France, as observed in the present study.

Female cancer patients getting radiation in and around the pelvic area are at risk of being infertile. High radiation doses may damage eggs leading to infertility and even lead to early menopause (**American Cancer Society, 2024**). The aetiology of female infertility is mostly influenced by oxidative stress, which is caused by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defences. Infertility is just one of several disorders that may be associated with oxidative stress (**Kaltsas *et al.*, 2023**). Due to these concerning findings, there is an increase in the number of original articles that shows interest in studying how radiation affects female reproductive organs including the ovary (n = 295), uterus (n = 88), accessory reproductive organs (n = 58), hormones (n = 52), monthly cycles (n = 43), oocyte and follicular count (n = 7), and apoptosis (n = 2). However, only 1 original article in the area of medicine was published in the topic of oocyte and follicular DNA fragmentation. Since the effects of ROS on male infertility have been researched more frequently in the past, the involvement of ROS in female infertility is contentious, the literature on the subject is scarce, and further research is needed (**Zaha *et al.*, 2023**). This is also evident from the present scientometric analysis that much more extensive scientifically designed research is needed in these areas.

Radiotherapy devices emit ionizing radiations that trigger dose-dependent molecular transformations (**Roldan-Valadez *et al.*, 2019**). A recent *in vitro* study showed heavy DNA damage to human endometrial stromal and epithelial cells within 30 minutes of radiation exposure (**Griffiths *et al.*, 2023**). Radiotherapy-induced damage not only impacts the ovarian follicles but also extends to the stroma of the ovaries. Such damage includes vascular injury, resulting in tissue atrophy and fibrosis (**Stroud *et al.*, 2009**). This is because human oocytes are highly sensitive to radiation with the LD_{50} estimated at < 2 Gy (**Wallace *et al.*, 2003**). The present scientometric analysis highlighted the fact that only two articles have been published in the area of radiotherapy investigating the molecular changes associated with female reproductive organs. In this light, a potential gap in research has been identified, highlighting the necessity for in-depth studies in the realm of radiotherapy specifically analyzing the effects of radiotherapy on the genomics and proteomics of female reproductive organs. It may lead to the identification of novel prognostic, diagnostic, and therapeutic biomarkers that could contribute to more effective management strategies.

Individuals undergoing radiotherapy are now advised to preserve their fertility (**Martynov *et al.*, 2020**). Developing and standardizing these protocols requires extensive research (**Goossens *et al.*, 2020**). This scientometric study reveals an overall increase in research related to radiotherapy and fertility preservation, with the first study published in 1993.

To minimize radiation exposure to reproductive organs during total body irradiation, gonadal shielding is practiced (**Rodriguez-Wallberg and Oktay, 2014**). For reproductive-aged women requiring pelvic or craniospinal radiation, ovarian transposition is beneficial. This technique surgically relocates the ovaries away from the radiation field, offering protection against premature ovarian failure and preserving fertility (**Marci *et al.*, 2018**). Oocyte cryopreservation has been a significant breakthrough for post-pubertal, unmarried female cancer patients. Freezing mature oocytes before gonadotoxic treatment offers the greatest potential for fertility preservation. The use of this method has increased with improvement in cancer treatment survival rates (**Pai *et al.*, 2021**). Our study shows that over 46% of publications are original articles, indicating a strong focus on identifying the best fertility preservation methods for female patients undergoing radiotherapy. Fertility preservation techniques such as gonadal shielding and oocyte cryopreservation are applicable for both post-pubertal and reproductive-aged women. Due to its ease of use and practicality, oocyte cryopreservation is the preferred choice for oncofertility patients (**ASRM, 2018**). Recently, artificial intelligence has been proposed to predict the outcomes of oocyte cryopreservation. However, long-term, well-powered prospective studies are needed to validate this approach (**Pai *et al.*, 2021**).

The collective synthesis of available literature thus enables us to concisely present the possible mechanism(s) by which radiotherapy affects female fertility. The primary mechanisms through which radiation impacts female reproductive health involve direct damage to ovarian follicles, disruption of the hypothalamic-pituitary-ovarian axis, and impairment of the uterine environment necessary for embryo implantation and foetal development. **Direct damage to ovarian follicles is through either of the following.**

i) Ovarian reserve depletion: Radiation exposure, especially to the pelvic area, can lead to the depletion of ovarian follicles. The human oocyte is highly sensitive to radiation, with a lethal dose for 50% of the population (LD_{50}) estimated at less than 2 Gy. Ionizing radiation induces double-strand breaks in DNA, leading to apoptosis of oocytes and granulosa cells, which are essential for follicle development and maintenance (**Bath *et al*., 2003; Wallace *et al.*, 2003)**.

ii) Vascular injury and fibrosis: Radiation can cause vascular injury within the ovarian stroma, leading to tissue hypoxia and fibrosis. This damage can impair blood flow to the ovaries, further reducing the ovarian reserve and leading to ovarian insufficiency (**Stroud *et al.*, 2009**).

Disruption of the hypothalamic-pituitary-ovarian axis constitutes another significant mechanism which is infliced through either of the following mechanisms.

i) Hormonal imbalance: Radiation can disrupt the hypothalamic-pituitary-ovarian axis, which is crucial for the regulation of reproductive hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This disruption can result in hormonal imbalances that affect ovulation and menstrual cycles, ultimately leading to infertility (**Wo and Vishwanathan, 2009; Dacal *et al*., 2022**).

ii) Premature menopause: High doses of radiation can accelerate ovarian ageing, leading to premature menopause. This condition is characterized by the cessation of menstrual cycles before the age of 40, resulting from the depletion of functional ovarian follicles (**American Cancer Society, 2024)**.

Radiotherapy can affect female fertility through the impairment of the uterine environment via the mechanisms listed below.

i) Uterine damage: Radiation can affect the structure and function of the uterus, making it less favourable for embryo implantation and growth. Damage to the endometrial lining can hinder the implantation process, while uterine fibrosis can

compromise the elasticity and contractility of the uterus, which are necessary for a successful pregnancy (**Griffiths *et al*, 2023**).

ii) Pregnancy complications: Women who have undergone pelvic radiation therapy during childhood or adolescence may face increased risks of pregnancy complications such as preterm labour, low birth weight, and placental abnormalities. These complications arise from radiation-induced damage to the uterine vasculature and endometrial integrity (**Green *et al.*, 2002**).

Oxidative stress and apoptosis is another significant pathway through which radiotherapy can induce infertility in the female through either of the following mechanisms.

i) Oxidative damage: Radiation generates ROS, which cause oxidative stress and cellular damage. In the ovaries, oxidative stress can lead to the apoptosis of oocytes and follicular cells, further diminishing the ovarian reserve and impairing fertility (**Kaltsas *et al.*, 2023)**.

ii) DNA fragmentation: Radiation-induced oxidative stress can result in significant DNA fragmentation in oocytes and follicles. This damage compromises the genetic integrity of the gametes, which is crucial for successful fertilization and embryo development (**Zaha *et al.*, 2023)**.

Finally, molecular and epigenetic changes can be brought about by radiotherapy that can eventually affect fertility in the female through either of the following routes.

i) Genomic and proteomic alterations: Radiation can induce molecular changes in the genomic and proteomic profiles of ovarian and uterine tissues. These changes may alter the expression of genes and proteins involved in reproductive processes. However, the current scientometric analysis reveals a paucity of studies specifically addressing these molecular changes, indicating the need for further research to fully understand their impact on female fertility.

ii) Epigenetic modifications: Exposure to radiation can also result in epigenetic modifications, such as DNA methylation and histone modification, which can affect gene expression without altering the DNA sequence. These epigenetic changes may play a role in the heritable effects of radiation exposure on fertility. More comprehensive studies are required to elucidate the extent and implications of these modifications.

Understanding these mechanisms is crucial for developing strategies to mitigate the adverse effects of radiation on female fertility. Approaches such as ovarian tissue cryopreservation, oocyte cryopreservation, and gonadal shielding during radiotherapy are being explored to preserve fertility in female cancer patients. Further research is needed to enhance these techniques and develop new interventions to protect reproductive health in women undergoing radiation therapy.

CONCLUSIONS

The present scientometric study marks the first endeavour to explore the correlation between radiotherapy and female fertility, as per our knowledge. Our scientometric analysis demonstrates a progressive surge in research on the subject of radiation therapy for female infertility over time. The primary emphasis of research has been on investigating the effects of radiotherapy on female reproductive organs and devising methods for fertility preservation. However, there is a crucial requirement for extensive studies to evaluate the influence of radiotherapy on female reproductive hormones, accessory reproductive organs, and the molecular changes associated with female reproductive organs. Additionally, further research is indispensable to formulate and enhance treatment plans that effectively safeguard women's fertility during cancer treatment.

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