Meta-analysis of factors associated with fertility concerns in young female cancer patients

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Abstract

Objective To identify the main influencing factors of fertility-related concerns among young female cancer patients through meta-analysis, so as to provide a basis for the design and implementation of intervention programs to alleviate patients' fertility concerns in the future.

Methods A comprehensive and systematic search was conducted in English databases including CBM, PubMed, Web of Science, Cochrane Library, Embase, and CINAHL Complete, as well as Chinese databases including CNKI, VIP Database, and Wanfang Database, supplemented by manual search. The search period was from database inception to February 2023. Two researchers independently performed quality assessment and data extraction. Meta-analysis of eligible literature was conducted using RevMan 5.4 software.

Results This study included a total of 24 articles with an overall sample size of 6,476 cases. Through meta-analysis, the pooled r-values of influencing factors were as follows: number of children [r=-0.178, 95%CI (-0.336, -0.01)]; marital status [r=-0.178, 95%CI (-0.327, -0.019)]; endocrine therapy [r=0.197, 95%CI (0.059, 0.309)]; I-131 therapy [r=0.178, 95%CI (0.039, 0.399)]; chemotherapy [r=0.244, 95%CI (0.187, 0.300)]; fertility intention [r=0.413, 95%CI (0.272, 0.544)]; fertility preservation [r=0.158, 95%CI (0.009, 0.300)]; depression [r=0.353, 95%CI (0.244, 0.454)].

Conclusion Demographic characteristics (number of children, marital status), disease-related factors (endocrine therapy, chemotherapy, I-131 therapy), depression, fertility intention, and fertility preservation are the main influencing factors of fertility-related concerns in cancer patients. In the future, enhanced attention should be paid to these risk factors for fertility concerns, and intervention strategies can be developed based on different influencing factors to reduce patients' levels of fertility-related concerns.

Full Text

Abstract

Objective: To identify the main influencing factors of fertility concerns in young female cancer patients through meta-analysis, providing an evidence base for designing and implementing interventions to alleviate these concerns.

Methods: A comprehensive systematic search was conducted in Chinese databases (CNKI, VIP, Wanfang, CBM) and English databases (PubMed, Web of Science, Cochrane Library, Embase, CINAHL Complete) from inception to February 2023, supplemented by manual searches. Two researchers independently performed quality assessment and data extraction. Meta-analysis of eligible studies was conducted using RevMan 5.4 software.

Results: Twenty-four studies with a total sample size of 6,476 cases were included. The pooled correlation coefficients (r) for influencing factors were: number of children [r = -0.178, 95% CI (-0.336, -0.01)]; marital status [r = -0.178, 95% CI (-0.327, -0.019)]; endocrine therapy [r = 0.197, 95% CI (0.059, 0.309)]; I131 therapy [r = 0.178, 95% CI (0.039, 0.399)]; chemotherapy [r = 0.244, 95% CI (0.187, 0.300)]; fertility intention [r = 0.413, 95% CI (0.272, 0.544)]; fertility preservation [r = 0.158, 95% CI (0.009, 0.300)]; depression [r = 0.353, 95% CI (0.244, 0.454)].

Conclusion: Demographic characteristics (number of children, marital status), disease-related factors (endocrine therapy, chemotherapy, I131 therapy), depression, fertility intention, and fertility preservation are the main influencing factors of fertility concerns in cancer patients. Future interventions should focus on these risk factors, with tailored strategies developed according to different influencing factors to reduce patients' levels of fertility concern.

Keywords: youth; cancer; female; fertility concerns; influencing factors; meta-analysis

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Introduction

According to GLOBOCAN 2020 data, approximately 19.3 million new cancer cases were diagnosed globally, with nearly 10 million cancer-related deaths. This burden is projected to reach 28.4 million new cases by 2040, representing a 47% increase from 2020 [**?**]. Cancer incidence is rising rapidly and showing a trend toward younger populations. For younger cancer patients, particularly surviving young women, fertility desires often persist. However, cancer treatments have direct and lasting detrimental effects on fertility, primarily through ovarian damage that leads to amenorrhea, premature menopause, and reduced reproductive capacity [**?**]. Research indicates that 40-80% of female cancer patients face infertility risks [**?**]. International studies have found that approximately 57% of young female cancer patients are troubled by fertility issues [**?**], with

80% of young cancer patients expressing a desire to have biological children [**?**]. Domestic research has similarly revealed high levels of fertility concerns among young cancer patients in China.

Fertility concern refers to anxiety regarding reproductive capacity, personal health, children' s health, and childcare following a cancer diagnosis [**?**]. The impact of fertility concerns on patients may exceed that of cancer itself and can persist for extended periods. Therefore, understanding the risk factors for fertility concerns represents a critical first step in alleviating them. While scholars have explored these influencing factors, study results vary across regions. This meta-analysis aims to clarify the factors influencing fertility concerns in young female cancer patients, providing an evidence base for clinical interventions.

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1. Materials and Methods

1.1 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study subjects were young female patients aged 18-45 years; (2) Patients were pathologically diagnosed with cancer/tumor; (3) Fertility concern levels were assessed using validated scales; (4) Study design was observational; (5) Language was English or Chinese. This study was approved by the Fudan University Evidence-Based Nursing Center (Registration number: ES20231000).

Exclusion criteria: (1) Conference abstracts; (2) Studies where full text was unavailable or represented duplicate publications; (3) Studies where data could not be extracted.

1.2 Literature Search Strategy

Chinese search terms included: "cancer,""tumor,""fertility,""fertility concern,""fertility worry,""influencing factor,""risk factor,"and "related factor."English search terms included: "neoplasms," "tumor," "cancer," "oncology," "carcinoma," "fertility concerns," "fertility-related concerns," "reproductive concerns," "factor,"" *influencing,*" *and* " *risk factor.*"

Databases searched: CNKI, VIP, Wanfang, PubMed, Web of Science, Cochrane Library, and Embase. The search timeframe spanned from database inception to February 2023, using a combination of subject headings and free terms. The search strategies are detailed in .

1.3 Literature Screening and Data Extraction

Two researchers independently screened literature according to the inclusion and exclusion criteria, removing obviously irrelevant or duplicate studies before conducting full-text reviews to finalize studies for meta-analysis. Disagreements

were resolved by a third reviewer. Extracted data included: title, author, publication year, study region, sample size, measurement tools, correlation coefficient (r) or standardized regression coefficient (β) values.

1.4 Literature Quality Assessment

Two researchers independently assessed study quality using the criteria recommended by the Agency for Healthcare Research and Quality (AHRQ) [**?**]. The 11-item checklist uses "yes," "no," or "unclear" responses, with a maximum score of 11 points. Each "yes" response received 1 point, while "no" or "unclear" received 0 points. Scores of 8-11 indicated high quality, 4-7 moderate quality, and 0-3 low quality. Disagreements were resolved through discussion.

1.5 Statistical Methods

Meta-analysis was performed using RevMan 5.4 software. Correlation coefficients (r) or β values (95% CI) for factors influencing fertility concerns in young female cancer patients were extracted as effect sizes. Heterogeneity was assessed using the Q test. If $P > 0.1$ and $I^2 < 50\%$, indicating no significant heterogeneity, a fixed-effects model was used; otherwise, a random-effects model was applied. $P < 0.05$ was considered statistically significant. Funnel plots were generated to assess publication bias. Sensitivity analyses were conducted using two methods: (1) comparing results between random-effects and fixed-effects models to assess robustness; (2) sequentially excluding each study to examine its impact on the pooled effect. Correlation strength was interpreted as: $r \leq 0.3$ (weak), $0.3 < r \leq 0.6$ (moderate), $0.6 < r \leq 0.8$ (strong), and $r > 0.8$ (very strong) [**?**].

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2. Results

2.1 Literature Search Results

The initial database search yielded 1,799 relevant studies: Cochrane Library (n = 3), PubMed (n = 527), Web of Science (n = 59), Embase (n = 370), CNKI (n = 442), Wanfang (n = 328), VIP (n = 32), and Chinese Biomedical Database (n = 38). After removing 246 duplicates, 1,553 studies remained. Title and abstract screening excluded 1,253 studies, leaving 30 for full-text review. Six studies were excluded due to inability to extract or convert data, resulting in 24 studies included in the final meta-analysis. The search process is illustrated in [Figure 1: see original paper].

2.2 Characteristics of Included Studies

The 24 studies included a total of 6,476 patients, comprising 22 cross-sectional studies [**?**] and 2 prospective cohort studies [**?**]. Nine studies [**?**, **?**] were rated

as high quality, and 15 [**?**, **?**] as moderate quality, indicating overall medium-to-high quality of included studies. Detailed characteristics and quality scores are presented in .

2.4.1 Meta-Analysis Results

Factors including endocrine therapy, age, and depression showed minimal heterogeneity ($P > 0.1$, $I^2 < 50\%$) and were analyzed using a fixed-effects model. All other factors demonstrated significant heterogeneity ($P < 0.1$, $I^2 \geq 50\%$) and were analyzed using a random-effects model. Meta-analysis results indicated that endocrine therapy, fertility intention, fertility preservation, number of children, I131 therapy, depression, chemotherapy, and marital status were all significant influencing factors of fertility concerns. Detailed results are summarized in .

2.4.2 Sensitivity Analysis

To test the stability and reliability of results, sensitivity analyses were performed on all included studies [**?**]. Using both random-effects and fixed-effects models yielded no substantial changes in pooled effect sizes for education level, endocrine therapy, quality of life, fertility intention, depression, number of children, I131 therapy, income, marital status, or employment, indicating robust findings. However, sequential exclusion of individual studies revealed changes in results for fertility preservation, disease stage, and chemotherapy. When Wang et al.' s study [**?**] was excluded, I^2 decreased from 90% to 0%, indicating this study was a major source of heterogeneity. When LjungmanL' s chemotherapy data [**?**] were excluded, I^2 decreased from 99% to 9%, suggesting this study substantially influenced the pooled effect for chemotherapy. When Jiang' s study [**?**] was excluded, I^2 for disease stage decreased from 92% to 0%, indicating it was the primary heterogeneity source. Effect sizes after exclusion are shown in .

2.4.3 Publication Bias

Funnel plot analysis was conducted for the three outcomes with the most included studies: education level, fertility intention, and number of children (see [Figure 2: see original paper]-[Figure 4: see original paper]). The asymmetrical distribution of included studies in the funnel plots suggests potential publication bias.

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3. Discussion

3.1.1 Fertility Intention and Fertility Preservation

Our findings indicate that patients with unmet fertility intentions experience higher levels of fertility concern, consistent with Qiao et al.' s research [**?**]. Fer-

tility intention refers to subjective reproductive desires, including preferences regarding number of children, gender, timing, spacing, and quality [**?**]. Rooted in fundamental individual needs and influenced by multiple factors [**?**], unmet fertility intentions generate varying degrees of anxiety when circumstances prevent fulfillment of these expectations. Patients with strong fertility intentions pay greater attention to the impact of cancer and its treatments on reproductive function, and this heightened focus may exacerbate concerns.

Patients who received fertility preservation interventions showed lower fertility concern levels. Fertility preservation encompasses appropriate nursing care, medication, and surgical procedures to protect fertility in women at risk of infertility, enabling future childbearing [**?**]. Multiple countries have established oncofertility preservation guidelines recommending pre-treatment fertility counseling [**?**]. France legally mandated fertility preservation in 2006, and the American Society of Clinical Oncology subsequently advocated legal protection of cancer patients' fertility [**?**]. However, guideline implementation remains inconsistent, requiring collaborative efforts from governments and healthcare professionals. International surveys reveal that only 5-24% of young Canadian female cancer patients received fertility preservation counseling before treatment [**?**], while most survivors in the US and UK never received any fertility preservation information [**?**]. Although methods such as embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation have been used abroad to alleviate fertility concerns, these approaches remain ethically and morally controversial [**?**]. Domestic fertility preservation technology development lags behind international progress and remains in the descriptive research phase, lacking exploration of underlying mechanisms. Therefore, governments should promote collaboration between oncology and reproductive medicine departments and establish fertility preservation training programs to enhance capacity among both cancer patients and healthcare professionals, facilitating shared decision-making in fertility preservation.

3.1.2 Depression

This study demonstrates that depressed patients experience higher levels of fertility concern, consistent with Wu et al.' s findings [**?**]. Cancer represents a significant negative life event that reduces quality of life, limits social activities, and increases financial burden, predisposing patients to depression. Depressive symptoms further reduce treatment adherence, creating a vicious cycle that impedes recovery. Qiao et al. [**?**] surveyed young female patients at a tertiary hospital in Urumqi, finding that depression severity increased with fertility concern scores; each one-point increase in fertility concern increased depression risk by 2.868-fold. After adjusting for confounders including occupation, family economic status, marital status, education level, and cancer type, fertility concern remained a primary risk factor for depression, with each one-point increase associated with a 2.423-fold increase in depression risk. Our study population of young female cancer patients is particularly vulnerable, as women

are more prone to self-esteem issues that elevate depression risk. Among the 22 cross-sectional studies, nine specifically focused on breast cancer, which may impair secondary sexual characteristics and lead to persistent feelings of guilt and low self-esteem, further fostering depression [**?**]. Healthcare providers should therefore monitor patients' psychological status and provide timely counseling. Clinical interventions such as mindfulness-based stress reduction, progressive breathing exercises, and meditation can help enhance self-identity and reduce depression levels.

3.1.3 Endocrine Therapy and Chemotherapy

Our findings indicate that patients requiring endocrine therapy and chemotherapy experience greater fertility concerns. Both treatments represent important postoperative adjuvant therapies that differentially impact young female patients. For young women with thyroid cancer, endocrine therapy significantly impairs sexual function, particularly manifesting as decreased libido, reduced sexual interest, and dyspareunia [**?**]. For breast cancer patients, standard endocrine therapy with tamoxifen (TAM), a selective estrogen receptor modulator, exerts anti-estrogenic effects in breast tissue but weak estrogenic effects in endometrial tissue, promoting endometrial cell proliferation and increasing risks of polyps, hyperplasia, and even malignancy with long-term use [**?**]. Chemotherapy inevitably damages ovarian function through cytotoxic drug-induced apoptosis of germ cells and vascular injury to ovarian stromal cells. Radiotherapy similarly induces and accelerates follicular atresia and granulosa cell apoptosis, impairing ovarian function and affecting fertility concerns [**?**].

3.1.4 I131 Therapy

I131 therapy is an important adjuvant treatment for thyroid cancer that significantly reduces recurrence and metastasis. However, the high radiosensitivity of gonadal tissue means that female patients receiving I131 therapy experience varying degrees of ovarian damage, including menstrual irregularities [**?**]. International reports indicate that radioactive iodine treatment affects menstrual regularity for up to six months post-treatment [**?**]. A qualitative study also revealed that 30% of patients were particularly concerned about whether radioactive iodine treatment would impact sexual activity, pregnancy, and breastfeeding [**?**].

3.1.5 Marital Status and Number of Children

Our study found that married young female cancer patients experienced higher fertility concern levels than unmarried patients, consistent with Tan et al.'s findings [**?**]. The family is an interactive system maintained through marital and blood relationships, where members' responsibilities and tasks vary across developmental stages, and individual behaviors, cognitions, and emotions influence one another. Married young female cancer patients bear key family responsibilities, and cancer significantly impacts their career prospects and weakens their

social and family roles, predisposing them to negative emotions and fertility concerns [**?**]. Additionally, married women' s greater emphasis on fertility issues [**?**] exacerbates their fertility concern levels. Fertility concern was inversely correlated with number of children, consistent with Wang et al.' s research [**?**]. In traditional Chinese culture, childbearing is considered essential for family completeness. Compared with single or divorced patients, married individuals face greater pressure and expectations regarding childbearing from spouses and family members [**?**], likely related to reproductive pressures and desires for children.

4. Limitations

This study has several limitations: (1) Only cross-sectional and prospective cohort studies were included, and only some influencing factors could be pooled. The inability to conduct subgroup analyses means some conclusions require further validation. (2) Potential publication bias may exist. (3) Variations in sample sizes and assessment tools across studies may contribute to heterogeneity. Future research should conduct multi-center, large-sample prospective cohort studies to increase effect sizes and enrich findings.

Conflict of Interest

All authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.