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Review

Younger Age as a Risk Factor for Gynecologic Cancer–related Lymphedema: A Systematic Review

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Abstract. *Background/Aim: Treatment of gynecologic cancers may lead to the development of lower limb lymphedema. As the course of lymphedema is chronic and progressive, early diagnosis plays a significant role in decreasing morbidity. Therefore, risk assessment is of utmost importance. In this study, we aimed to investigate the impact of age on lymphedema development after treatment for gynecologic cancers. Materials and Methods: The search of 3 databases (PubMed, Scopus, and Cochrane) revealed 7 relevant articles, which reported either odds ratios or hazard ratios as an outcome measure. Results: A positive relationship between younger age and lower limb lymphedema was shown by 3 articles, while 2 noted increased incidence with older age. The remaining articles reported no significant relationship. Conclusion: Younger age is a risk factor for gynecologic cancer–related lymphedema. However, as individual studies have not included all types of gynecologic cancers, results may not be generalizable.*

Lymphedema (LE) is a localized disease caused by an imbalance between interstitial lymphatic fluid formation and lymphatic outflow. Depending on its etiology, lymphedema may be primary or secondary and transient or permanent (1, 2). Secondary lymphedema has several risk factors such as radiotherapy, higher body mass index, lymph node dissection, and the higher number of removed lymph nodes (3, 4). Though predisposing factors differ for various types of cancer, several of them are shared by gynecologic cancers. Identification of these factors is essential for risk stratification. In this way, appropriate measures can be taken to prevent lymphedema development in high-risk patients.

The association of many risk factors with lymphedema is well established, but the relationship between lower limb lymphedema (LLL) occurrence and age is not clearly described. The purpose of our study was to determine the effect of age on the development of LLL in gynecologic cancer survivors.

Materials and Methods

Study selection. A search for clinical studies was done using PubMed, Scopus, and Cochrane databases using the search strategy [“lymphoedema”(All Fields) OR “lymphedema”(MeSH Terms) OR “lymphedema”(All Fields)] AND [“Age”(Journal) OR “Age (Omaha)”(Journal) OR “Age (Dordr)”(Journal) OR “Adv Genet Eng”(Journal) OR “age”(All Fields)] AND [“risk factors”(MeSH Terms) OR “risk”(All Fields) AND “factors”(All Fields)] OR]“risk factors”(All Fields)].

Inclusion criteria. Studies of gynecologic cancer–related lymphedema (GCRL) reporting odds ratios (ORs), hazard ratios (HRs), or relative ratios were included.

Exclusion criteria. Systematic reviews, meta-analyses, case reports, editorials, reviews, and GCRL articles that did not report ORs, HRs, or relative ratios were excluded.

Data abstraction. Two authors did independent searches and verified the article selection (March 30, 2020). Disagreements in study selection were solved with the help of a third author. Author name, year of publication, country, study design, follow-up period, number of patients, age groups, mean age, and association with lymphedema formation were extracted (Table I).

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Table I. *Summary of the studies included in the review.*

Author, Year, Country	Type of study	Patients	Mean age	Etiology	Age	Association	*p*-Value	Diagnostic test	Outcome measure	Center	Follow-up
Yoshihara *et al.* 2020, Japan	Retrospective	711	50.2	Endometrial, cervical, and ovarian cancer	Age <50 *vs.* ≥50	Younger age higher incidence	*p*<0.001	Physical examination	OR=1.919 (multivariate)	Multicenter	Median 5.05 years
Carlson *et al.* 2020, USA	Prospective	914	61; 44; 58	Endometrial, cervical, and vulvar cancer	Age (years)	Younger age higher incidence	*p*=0.0467	Circumferential measurements Stemmer sign	OR=0.816	Multicenter	2 years
Kuroda *et al.* 2017, Japan	Retrospective	264	54.95	Uterine corpus, cervical, ovarian, tubal, and vaginal cancer	Age <56 *vs.* ≥56	No association	*p*=0.154	Medical records	HR=1.353	Unicentral	Median 5.66 years
Deura *et al.* 2014, Japan	Retrospective	126	55	Endometrial, cervical, ovarian, vulvar, and vaginal cancer	Age <55 *vs.* ≥55	Older age higher incidence	*p*=0.028	Circumferential measurements	OR=12.3	Unicentral	Median 1.33 years
Hinten *et al.* 2011, The Netherlands	Retrospective	164	71	Vulvar squamous cell carcinoma	Age (years)	Younger age higher incidence	*p*<0.05	Medical records	OR=0.95	Unicentral	Median 4.2 years
DA Cirik *et al.* 2015, Turkey	Retrospective	99	61.2	Vulvar cancer	Age <65 *vs.* ≥65	No association	*p*=0.079	Medical records	OR=0.29	Unicentral	>5 years (annually)
Hong *et al.* 2002, USA	Retrospective	228	53	Cervical cancer	age <60 *vs.* ≥60	Older age Higher incidence	*p*=0.105	Physical examination	OR 1.755	Unicentral	Minimum 3 years

Results

Of 508 articles published between 1974 and 2020, 7 met the inclusion criteria. The studies involved a combined total of 2,506 uterine corpus, endometrial, cervical, vaginal, vulvar, ovarian, and tubal patients. The average age was 55.94 years. To calculate the mean age, reported medians were converted to means using the method suggested by Hozo *et al.* (5). A diagnosis of lymphedema was obtained either through medical record extraction (3 studies) or patient examination [*i.e.*, circumferential measurement (2 studies), physical findings (2 studies)]. The researchers used different methods to diagnose lymphedema [circumferential measurements (cm), physical symptoms noted by a physician, self-report based on subjective symptoms].

Substantial heterogeneity was observed regarding age groups, patient selection, and follow-up duration. Age groups were described as older or younger than a given age. Patients were chosen either from one cancer type or a combination of different cancer types. Outcome assessment also differed among studies, ranging from self-filled questionnaires to medical records to regular follow-up appointments.

Yoshihara *et al.* (6) studied 711 patients with endometrial, cervical, or ovarian cancer and found that age younger than 50 years increased the likelihood of experiencing post-cancer, late-onset LLL (≥5 years: OR=1.919; *p*=0.001; ≥10 years: OR=3.657; *p*<0.001). Nearly one-third (29.4%) of their patients had lymphedema 10 or more years after intervention (6). Carlson *et al.* (7) identified older age as the only significant risk factor for their patient group of endometrial, cervical, and vulvar cancer survivors (OR=0.816; *p*=0.0467) (7). Though not significant in univariate analysis, Deura *et al.* (8) found a statistically significant OR value (12.3) in multivariate analysis for patients aged 55 years and older. The study population consisted of endometrial, cervical, ovarian, vulvar, and vaginal cancer survivors (8). In the study by Kuroda *et al.* (4) for patients aged 56 and older, HR was 1.353. However, the p-value was more than 0.05 (*p*=0.154) (4). Hong (9) described a higher incidence of LE in cervical cancer patients who were 60 years and older (41% vs. 28%; *p*=0.08). However, the OR of 1.755 was not statistically significant (*p*=0.105) (9). Hinten *et al.* (10) identified younger age as an independent risk factor for LE

development after the treatment of vulvar cancer (OR=0.95; $p<0.05$) (10). Cirik *et al*. (11) reported a nonsignificant OR of 0.29 for the patients aged 65 and older (CI=0.07-1.24). They attempted to explain the higher incidence rates with the following hypothesis: Unlike older individuals, younger people usually have a high level of activity before treatment; after the interventions, they make an abrupt change to a more sedentary lifestyle, which makes them prone to LLL development (11).

Discussion

The development of different types of LE usually shares 1 of 3 types of mechanisms described in the literature: dynamic, mechanical, and safety valve. Dynamic LE, *i.e*. high-volume lymphedema, occurs when filtration surpasses the transport capacity of lymphatics. Mechanical, or low-volume lymphedema, develops due to interference with lymph flow (*e.g*., obstruction) (12, 13). The safety valve LE is a combination of the first two types.

Secondary LE has been defined as "all causes of lymphedema caused by disease not originating in the lymph conducting elements of the vessels and nodes" (14). Cancer-associated LE is the most frequent cause of lymphedema in the industrialized world. Obstruction can be caused by the tumor itself, by micrometastasis, or by treatment modalities (*e.g*., radiation, chemotherapy, and surgical intervention) (2). Coping with a chronic, progressive, and incurable disease following a physically and emotionally distressing cancer diagnosis and treatment can give rise to depression, anxiety, and other psychological problems (15).

Depending on the type of treatment received, the incidence of LE after gynecologic cancers may range from 0% to 70% (16). The time from treatment for gynecologic malignancies to LE occurrence differs considerably among patients. In the study by Yoshihara *et al*. (3) the incidence of lymphedema was most frequently observed in the first year after treatment. They reported some cases of super-late–onset LLE that occurred 20 years or later post-treatment (3). In another study, 60.3% of patients developed LLE in the first year after surgery (3).

Limitations

The main limitation of this study is the small number of articles studied. The exclusive use of the English-language in published studies may have introduced language and publication bias. Another limitation is the interpretation of data of patients suffering from different cancers. Age may increase or decrease the risk for LE development for some gynecologic cancers, but not for others.

This review indicates that younger patients are more likely to be affected by GCRL. However, due to the limited number of publications meeting our inclusion criteria, the results of this systematic review may not be clinically significant. Patient stratification into groups based on cancer type would increase the quality of papers and the reliability of the results.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Gunel Guliyeva: Project development; Data collection; Data analysis; Manuscript writing; Maria T. Huayllani: Project development; Data collection; Data analysis; Manuscript writing; Francisco R. Avila: Data collection; Manuscript editing; Daniel Boczar: Data analysis; Manuscript editing; Xiaona Lu: Manuscript editing and revision; Antonio J. Forte: Project development; Manuscript editing and revision.

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