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Global distribution pattern of histological subtypes of epithelial ovarian cancer: A database analysis and systematic review

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HIGHLIGHTS

- There existed significant variations of subtype distribution among countries and regions in the world.
- Serous and endometrioid subtype showed less distribution variation, while larger differences were seen in mucinous and clear cell subtype.
- A guide map for selecting countries or regions to implement clinical trials for epithelial ovarian cancer was provided.

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ABSTRACT

Background. Epithelial ovarian cancer is basically a heterogeneous disease with different chemosensitivity and distinct molecular alternations for each histological subtype. In order to assess whether the results of clinical trials can be extrapolated to a new country, it is critical to first examine whether the relative frequencies is homogenous across countries.

Methods. Cancer registry database from a single institution in Taiwan combined with systematic review of the global literature on the relative frequencies of histological subtypes between 2003 and 2012 was provided.

Results. Of 175 titles identified, 41 studies met inclusion/exclusion criteria. Globally, for each subtype, the median value of relative frequencies for serous subtype was 45.0%, with the Philippines (16.0%), Indonesia (22.7%), and Brazil (30.1%) as the three lowest countries and South Africa (68.0%), Greece (71.5%), and India (86.7%) as the three highest countries; for mucinous subtype, 11.4%, Italy (3.0%), Australia (3.4%), and Japan (5.4%) were the three lowest countries, while Indonesia (29.1%), Singapore (30.3%), and South Korea (38.6%) were the three highest countries; for endometrioid subtype, 12.6%, India (1.6%), Greece (5.7%), and Portugal (7.6%) were the three lowest countries, while Taiwan (24.8%), Egypt (25.0%), and Austria (25.5%) were the three highest countries; and for clear cell subtype, 5.3%, Pakistan (1.0%), Iran (2.0%), and Brazil (2.1%) were the three lowest countries while Thailand (16.0%), Taiwan (16.8%), and Spain (18.8%) were the three highest countries.

Conclusions. Relative frequencies of subtypes were not homogenous across countries. This diversity may reflect the geographical and ethnic variations. Globally, epithelial ovarian cancer is a heterogeneous disease with a heterogeneous distribution pattern.

Introduction

Among the gynecological malignancies, ovarian cancer is the leading cause of mortality in developed countries with estimated 225,500 new cases and 140,200 deaths worldwide [1]. In the United States, it is estimated that 22,240 women will be diagnosed with ovarian cancer in 2013 among whom 14,030 will die [2].

The majority of ovarian cancer is of epithelial origin. The major histological subtypes of epithelial ovarian cancer include: serous, mucinous, endometrioid, clear cell, undifferentiated and unclassified [3]. Each of these subtypes is genetically distinct with unique molecular pathogenesis and different susceptibility to chemotherapeutic agent. Nevertheless, the regulatory mechanisms underlying this heterogeneity remain poorly understood [4,5]. Currently, clinical trials do not differentiate these subtypes but treat them as a homogeneous group. As a consequence, the results are difficult to interpret as it is not clear whether

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the findings are applicable to a specific subtype or to another country if the subtype distribution pattern is not consistent between countries.

Generally, U.S.- or E.U.-based pivotal multicenter clinical trials for epithelial ovarian cancer seldom include clinical centers in Asia, Central and South America, and Africa, which are referred as the "new region" under the setting of bridging trials. Results of clinical trials are often generalized without further investigation, and the findings are used to support new drug applications in the new regions [6].

Due to the fact that epithelial ovarian cancer is a heterogeneous disease with four major subtypes, it is imperative for researchers and clinicians to know the distribution pattern of the histological subtypes and the potential differences between countries or populations when evaluating the applicability of trial results to a new region. In the current study, we aimed to conduct a global systematic review to assess the distribution pattern of subtypes of epithelial ovarian cancer. Relative frequencies of each subtype were calculated using data from cancer registries, controlled clinical trials, cohort studies, or studies of archives of surgical samples. Furthermore, by employing cluster analysis, we explored the aggregation patterns among the countries examined on the basis of their similarities in subtype distributions.

Methods

Database retrieval

Electronic database from a total of 648 primary epithelial ovarian cancer was retrieved, which is a stably constructed registration system of consecutively treated patients of ovarian cancer, set up in Taipei Veteran General Hospital between January 2003 and December 2012. All information was collected under protocols approved by a hospital Institutional Review Board.

Search strategy of systematic reviews

The systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [7]. For included observational studies, Meta-analysis of Observational Studies in Epidemiology (MOOSE) was further followed [8]. A comprehensive computerized systemic review of published reports, including cancer registry database, randomized controlled trials, cohort studies, and studies of surgical specimens, was performed by searching the following databases: Medline, EMBASE, Cancerlit, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ISI Web of Science, and Google Scholar. The key search terms included 'epithelial ovarian cancer,' 'serous,' 'mucinous,' 'endometroid,' 'clear cell,' in combination with the following terms: 'cohort,' 'controlled trials,' 'database,' 'survey,' 'epidemiology,' 'registry,' 'specimens,' and 'surgical archives'. The search was limited to human studies published in English from January 1990 to December 2012.

Inclusion and exclusion criteria

Included were studies that reported the distributions of all subtypes (serous, mucinous, endometroid, clear cell, and others) of epithelial ovarian cancer. We excluded studies (i) with inadequate sample size, defined as less than 50 cases or surgical archives, (ii) missing cases in any one of four major subtypes, (iii) subtype-specific studies, (iv) animal xenograft studies using human cancer cell lines, and (v) abstracts, letters and posters where the full study was not published.

Screening and data extraction

The systematic search described above was completed by March, 2013. Two independent reviewers (P.L.S. and C.M.C.) assessed the potential relevance of all titles and abstracts identified from the electronic searches. Full articles were retrieved for further assessment when the abstracts indicated that they might meet the inclusion criteria. Disagreements were resolved through discussion and consensus. A third reviewer (M.S.Y.) was consulted in case of persisting disagreement.

The reviewed data were extracted and entered on to an ad hoc standardized data entry form by each reviewer. Data extracted for comparison included study of origin (continent/country), year of publication, research design, number of cases for each subtype, length of recruitment period, source of information. Minor subtype (e.g. transitional and squamous), undifferentiated and non-otherwise specified carcinoma, are categorized under "others" category. Relative frequencies of each subtype were calculated for each retrieved article. The definition of relative frequency points to the relative percentage of one subtype to the overall epithelial subtypes. As such, the sum of relative frequency of the four major subtypes may not be equal to 100% due to the presence of others (including squamous, transitional cell, and undifferentiated carcinoma).

As a rule, we selected one representative study from each country or region for final analysis. For Europe, because several randomized trials are purely derived from European countries, therefore we decided to include these studies for the purpose of comparison. For the United States, because of existing Surveillance, Epidemiology and End Results (SEER) program, therefore we decided not to include randomized clinical trials. Instead, we present two SEER results for the purpose of comparison. In decreasing order, the priority of study selection is database analysis, followed by randomized controlled trials, then by observational studies, and finally by studies of surgical archives.

Assessment of methodological quality

The quality of randomized controlled trials was evaluated using validated Jadad scoring system which ranges from 0 (bad) to 5 (good). On the basis of Jadad scoring, we dichotomized the quality of reporting into poor (score < 3) or good (score ≥ 3) [9]. Quality of observational studies (e.g. database analysis, cohort study, and surgical archives) was scored according to the Newcastle–Ottawa Quality Assessment Scale which ranges from 1 (poor) to 9 (excellent) [10]. Because there are no descriptive anchors for this scale except the lowest and highest score, we decided to classify studies with a total score equal to or greater than 7 as high-quality studies.

Statistical analysis

Studies were grouped using the United Nations classification, which categorizes the world into 5 macrogeographical (continental) regions and 22 geographical subregions [11]. Agreement on the inclusion of studies was assessed using a kappa statistic. Relative frequency of each subtype for each included studies was presented by continent. The coefficient of variation (CV) was calculated by dividing the standard deviation by the mean measurement of relative frequency. Discrepancy of relative frequency between countries was assessed by chi-square test.

Hierarchical cluster analysis was conducted to classify countries according to the distributions of all subtypes by calculating the distances according to the closeness of between-country distances. In this analysis, we used an agglomerative clustering procedure based on standardized Euclidean distances and the average linkage algorithm [12]. All countries were represented by their relative positions on a cluster tree (dendrogram) that shows the similarities and dissimilarities between countries. The merging of countries with similar features leads to the formation of a cluster, where the length of the branch indicates the degree of relation. Thus, countries with tightly related features appear closer together, while the degree of separation in the cluster tree increases with further dissimilarity. In order to calculate the distances between all variables in the analysis, they were further standardized by transforming the data to have a mean $= 0$ and a variance $= 1$. All statistical tests were two-sided with a significance level of p-value of 0.05