INTRODUCTION

Borderline ovarian tumors (BOTs) or ovarian tumors of low malignant potential were first described by Taylor in 1929 [1]. BOTs account for 10–15% of all ovarian cancers; they typically affect younger women, as compared with invasive epithelial ovarian tumors, and are mostly diagnosed at earlier stages, which results in a more favorable prognosis. However, a small fraction of BOTs such as advanced-stage diseases with invasive implants are associated with poor prognosis and high recurrence rates of 20–50% [2]. BOTs can be classified histologically according to their epithelial characteristics as serous, mucinous, endometrioid, clear cell or Brenner tumors. As the various histologic types exhibit striking differences in clinical presentation and behavior [3–5], determination of the cell type is critical in the assessment of BOTs, and the different types should be evaluated separately.

Interestingly, there appears to be a difference in the histologic distribution of BOTs according to geographic region. Studies in the USA [6], France [7], and Italy [8] have reported serous-type BOTs as the most common (60–74), while studies in Korea [9] and Japan [10] have reported mucinous-type BOTs as the most common (68–76). However, these studies are too limited in number to reach firm conclusions about regional differences. Therefore, we performed a systematic review of the literature to understand this phenomenon.

Histologic distribution of borderline ovarian tumors worldwide: a systematic review

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Objective: The histologic types of borderline ovarian tumors (BOTs) exhibit striking differences in clinical behavior and prognosis. Yet, there is no information available on the histologic distribution of BOTs according to geographic region. The purpose of this study was to systematically review this issue worldwide.

Methods: A comprehensive search of the literature was conducted using electronic databases. Studies were eligible if BOTs were investigated and the histologic distribution of the data was shown. The studies were grouped by geographic region and totaled by country.

Results: Of 487 potentially relevant studies, 51 met our inclusion criteria, as follows: 8 studies from North America (2 countries); 26 studies from Europe (14 countries); 7 studies from the Middle East (3 countries); and 10 studies from East Asia (5 countries). The histologic distribution of BOTs was considerably different in different parts of the world, but follows specific patterns. In general, serous-type BOTs were the predominantly identified histology in North America, the Middle East, and Europe, while mucinous-type BOTs predominated in East Asia.

Conclusion: Significant geographic variation is evident among BOT histology in different parts of the world. More research is needed to understand this phenomenon.

Keywords: Borderline ovarian tumor, Histology, Low malignant potential, Systematic review
review of published data regarding the worldwide histologic distribution of BOTs to determine whether or not a difference exists according to geographic region.

MATERIALS AND METHODS

A comprehensive search of the literature was conducted using electronic databases (Medline, Embase, and Cochrane Library). The title and abstract search terms used were as follows: borderline tumor, borderline tumour, borderline neoplasm, low malignant potential, and ovarian, ovary. These terms were also searched as keywords and medical subheadings (MeSH). Each database was searched from its inception to its most recent update as of 5 April 2011.

1. Study selection: inclusion/exclusion criteria

Two investigators (TS and YYL) independently screened the titles and abstracts in duplicate, using standardized techniques. A study was eligible if BOTs were investigated and if the distribution of tumor histology was included (e.g., serous 50; mucinous 40; and others 10). Even if a full text manuscript was written in a non-English language, the study was eligible if data on the histologic distribution of BOTs was included in the abstract written in English. The exclusion criteria were as follows: study subjects were not representative of an entire population but rather of a specifically defined population (e.g., women with advanced-stage BOTs or women with serous BOTs); the study did not present new data (e.g., case reports, review articles, editorials, and letters); and non-human studies. The abstract was evaluated to determine whether or not a study contained quantitative information on the distribution of tumor histology. If review of the abstract did not permit this determination, the full paper was evaluated. Final inclusion and exclusion were based on the full-text manuscripts. To broaden the search, a secondary strategy was carried out, reviewing reference lists of all available primary eligible studies. In the event of disagreement between the two investigators, the disagreement was solved by consensus.

2. Data extraction

Two independent investigators used a piloted data extraction form to collect all relevant data from the studies, including author, year of publication, country of study, type of cohort (single center, multicenter, and population-based), sample size, and information on the histologic distribution of BOTs. Data were entered into an electronic database so that duplicate entries existed for each study; when the two entries did not match, consensus was reached through discussion. We did not contact the authors of studies for any further information.

3. Data synthesis

The included studies were grouped according to geographic region (e.g., North America, Europe, the Middle East, and East Asia). These regions were then divided into subgroups according to the country studied. If an identical author or group reported several studies using the same or an overlapping cohort, we selected the more recent, larger study and excluded the other. In order to schematically illustrate the worldwide histologic distribution of BOTs, data from each study were totaled according to country, regardless of the design or size of the study, and a world map was created representing the most common histology according to country.

RESULTS

1. Study selection and study characteristics

Initially, 487 studies were identified in the 3 online databases, after the removal of duplicates. Of the 487 studies, 123 were excluded because the title and abstract revealed no relevance to the current review, and 302 studies were excluded because they did not meet the inclusion criteria after reading the full text. Finally, 2 studies were added by searching the reference lists of all primary studies, and 13 studies were excluded for using the same or overlapping cohorts, leaving 51 studies eligible for inclusion in the systematic review. The full selection process is summarized in Fig. 1 showing the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the systematic review [11].

Overall, the 51 eligible studies included 8 studies from North America (2 countries: Canada and USA), 26 studies from Europe (14 countries: Norway, Sweden, Finland, Denmark, Netherlands, Belgium, Germany, Bulgaria, Poland, Switzerland, France, Italy, Spain, and Greece), 7 studies from the Middle East (3 countries: Turkey, Israel, and Iran), and 10 studies from East Asia (5 countries: China, Singapore, Taiwan, Korea, and Japan). Thirty-five studies (68) used a database from a single center, 8 (16) used a database from multi-centers, and 8 (16) used a population-based database (a regional or national cancer registry). The individual studies are described in Table 1.

2. Mapping the distribution of tumor histology

Information from the review was used to create a world map illustrating the histologic distribution of BOTs according to country (Fig. 2). Serous histology was the most common type reported in North America, Europe, and the Middle East.
contrast, the mucinous histology was the most common type reported in East Asia. Of 14 European countries, 11 (79%) reported serous-type BOTs as the most common, and 3 (21%; Spain, Denmark, and Netherlands) reported mucinous-type BOTs as the most common.

DISCUSSION

Our review is the first to systematically review, categorize, and map the worldwide histologic distribution of BOTs. The main finding is that the histologic distribution of BOTs is considerably different in various parts of the world, but follows specific patterns. In general, serous-type BOTs were the predominantly identified histologic type in North America, the Middle East, and most of Europe. In contrast, mucinous-type BOTs predominated in East Asia and parts of Europe. No data were available for other geographic regions of the world.

Although our study found that there is a difference in the histology of BOTs according to geographic region, it is not yet clear which factors are related to this phenomenon. Lifestyle factors appear to be attributable. According to a recent study conducted in Denmark [12], both a history of breastfeeding and use of oral contraceptives reduced the risk of BOTs, the effect being most pronounced for serous tumors. Increasing body mass index was associated with an increased risk of serous tumors (OR, 1.05 per BMI unit; 95 CI, 1.00 to 1.10), whereas current smoking was a strong risk factor for mucinous tumors alone (OR, 2.10; 95 CI, 1.22 to 3.60). Smoking in particular has been found in several studies to be a risk factor associated with benign, borderline, and invasive mucinous ovarian tumors [13-15]. Some studies have reported a strong association
Table 1. The 51 studies included in this systematic review

| Author, year | Country    | Data source | No.  | Serous | Mucinous | Others |
|--------------|------------|-------------|------|--------|----------|--------|
| Anfinan, 2010 [17] | Canada     | Single center | 138  | 70 (51) | 45 (33)  | 23 (17) |
| Rice, 1992 [18]   | USA        | Single center | 38   | 24 (63) | 13 (34)  | 1 (3)  |
| Morris, 2009 [19] | USA        | Single center | 43   | 26 (60) | 17 (40)  | 0 (0)  |
| Rettenmaier, 2010 [20] | USA         | Single center | 78   | 51 (65) | 17 (22)  | 10 (13) |
| Vine, 2001 [21]  | USA        | Multicenter  | 151  | 79 (52) | 60 (40)  | 12 (8) |
| Rao, 2005 [22]   | USA        | Multicenter  | 249  | 176 (71) | 57 (23)  | 16 (6) |
| Shih, 2011 [6]   | USA        | Single center | 266  | 196 (74) | 64 (24)  | 6 (2)  |
| Mink, 2002 [23]  | USA        | Population-based | 2,211 | 1,374 (62) | 793 (36) | 44 (2) |
| Odgaard, 2007 [24] | Norway    | Single center | 112  | 57 (51) | 53 (47)  | 2 (2)  |
| Riman, 2001 [25] | Sweden     | Population-based | 193  | 110 (57) | 81 (42)  | 2 (1)  |
| Akeson, 2008 [26] | Sweden     | Population-based | 399  | 219 (55) | 171 (43) | 9 (2)  |
| Kumpulainen, 2007 [27] | Finland  | Multicenter | 65   | 37 (57) | 27 (42)  | 1 (1)  |
| Hannibal, 2011 [28] | Denmark | Population-based | 5,079 | 2,235 (44) | 2,539 (50) | 305 (6) |
| Engelen, 2000 [29] | Netherlands | Single center | 36   | 13 (36) | 22 (61)  | 1 (3)  |
| Kolwijck, 2009 [30] | Netherlands | Single center | 123  | 43 (35) | 80 (65)  | 0 (0)  |
| Verbruggen, 2008 [31] | Netherlands | Multicenter | 93   | 36 (39) | 57 (61)  | 0 (0)  |
| Donnez, 2003 [32] | Belgium    | Single center | 75   | 37 (50) | 36 (48)  | 2 (2)  |
| Fotopoulou, 2009 [33] | Germany | Single center | 51   | 39 (76) | 12 (24)  | 0 (0)  |
| Ivanov, 2002 [34] | Bulgaria   | Single center | 43   | 28 (65) | 15 (35)  | 0 (0)  |
| Makaarrevicz, 2003 [35] | Poland    | Single center | 106  | 58 (55) | 48 (45)  | 0 (0)  |
| Bouchardy, 2008 [36] | Switzerland | Population-based | 130  | 71 (55) | 59 (45)  | 0 (0)  |
| Levi, 1999 [37] | Switzerland | Population-based | 176  | 102 (58) | 72 (41)  | 2 (1)  |
| Camatte, 2004 [7] | France     | Single center | 101  | 60 (60) | 30 (30)  | 11 (10) |
| Fauvet, 2005 [38] | France     | Multicenter  | 358  | 187 (52) | 138 (39) | 33 (9) |
| De iaco, 2009 [39] | Italy      | Multicenter  | 168  | 102 (61) | 40 (24)  | 26 (15) |
| Maneo, 2004 [40] | Italy      | Single center | 62   | 42 (68) | 18 (29)  | 2 (3)  |
| Palomba, 2007 [41] | Italy      | Single center | 32   | 29 (91) | 3 (9)    | 0 (0)  |
| Romagnolo, 2006 [8] | Italy      | Multicenter  | 113  | 75 (66) | 35 (31)  | 3 (3)  |
| Zanetta, 2001 [42] | Italy      | Single center | 339  | 205 (60) | 124 (37) | 10 (3) |
| Benito, 2010 [14] | Spain      | Single center | 163  | 68 (42) | 91 (56)  | 4 (2)  |
| Cusido, 2007 [43] | Spain      | Multicenter  | 457  | 208 (46) | 222 (49) | 26 (6) |
| Martin Jimenez, 1994 [44] | Spain     | Single center | 31   | 12 (39) | 16 (48)  | 3 (13) |
| Liapis, 2008 [45] | Greece     | Single center | 93   | 49 (53) | 39 (42)  | 5 (5)  |
| Economou, 2005 [46] | Greece     | Single center | 32   | 17 (53) | 11 (34)  | 4 (13) |
| Ayhan, 2005 [47]  | Turkey     | Single center | 100  | 54 (54) | 39 (39)  | 7 (7)  |
| Boran, 2005 [48] | Turkey     | Single center | 139  | 84 (60) | 49 (35)  | 6 (5)  |
| Kanat-Pektas, 2011 [49] | Turkey  | Single center | 123  | 58 (47) | 61 (49)  | 4 (4)  |
| Pirimoglu, 2008 [50] | Turkey | Single center | 57   | 29 (51) | 26 (45)  | 2 (4)  |
| Gottlieb, 2005 [51] | Israel     | Population-based | 233  | 155 (67) | 69 (30)  | 9 (3)  |
| Iscovitch, 1998 [52] | Israel     | Population-based | 222  | 153 (69) | 64 (29)  | 5 (2)  |
| Behtash, 2004 [53] | Iran       | Single center | 38   | 29 (76) | 8 (21)   | 1 (3)  |
| Li, 2003 [54]    | China      | Single center | 34   | 13 (38) | 18 (51)  | 3 (11) |
| Ren, 2009 [55]   | China      | Single center | 234  | 101 (43) | 113 (48) | 20 (9) |
| Zhang, 1998 [56] | China      | Single center | 70   | 21 (30) | 46 (66)  | 3 (4)  |
| Wong, 2007 [57]  | Singapore  | Single center | 247  | 65 (26) | 169 (68) | 13 (4) |
| Wu, 2009 [58]    | Taiwan     | Single center | 233  | 61 (26) | 157 (67) | 15 (7) |
| Park, 2009 [9]   | Korea      | Single center | 360  | 112 (31) | 245 (68) | 3 (1)  |
| Kim, 2009 [59]   | Korea      | Single center | 63   | 21 (33) | 42 (67)  | 0 (0)  |
| Kokawa, 2009 [10] | Japan      | Single center | 222  | 47 (21) | 169 (76) | 6 (3)  |
| Tamakoshi, 1997 [60] | Japan   | Single center | 150  | 56 (37) | 90 (60)  | 4 (3)  |
| Yokoyama, 2006 [61] | Japan     | Single center | 121  | 27 (22) | 91 (75)  | 3 (3)  |
between smoking and these three types of tumors, suggesting that smoking is involved early in the neoplastic process. It has been speculated that the relationship between cigarette smoking and the development of mucinous tumors could be due to the similarity of mucinous tumors to gastrointestinal mucosa. Cigarette smoking has consistently been associated with mucinous gastrointestinal tract cancers such as those of the stomach and pancreas [12,13].

The results of the current study have potential implications for the treatment of choice in patients with BOTs. According to recent studies conducted in France [3,16], mucinous BOTs, unlike serous BOTs, do not appear to be a “safe” disease, with a 13 cumulative risk of recurrence in the form of invasive carcinoma at 10 years [16]. The authors of a previous study concluded that the use of salpingo-oophorectomy rather than cystectomy is preferred during conservative surgery for patients with mucinous BOTs because salpingo-oophorectomy decreases the risk of recurrence and does not impair fertility [3]. Therefore, in regions with a high incidence of mucinous BOTs, cystectomy should not be considered as a conservative surgery without the confirmation of tumor histology through intraoperative frozen section analysis. The results of the current study also have potential implications for the diagnosis of BOTs. Being aware of the histological distribution of BOTs over the world would help the pathologists who are to evaluate the ovarian masses with a high index of suspicion for BOTs.

This review has several limitations that merit attention. First, we tried to search many studies as possible through electronic databases, but many of which were not available. Only peer-reviewed articles were included in the systematic review. Second, this review may also be subject to language limitations, although we did not exclude a study if the abstract was written in English without regard to the language of the main text. Third, the histological distribution of BOTs within a certain country/geographical area can be biased by the existence of women belonging to different ethnic groups. That is, a relevant study conducted in Turkey would review the women with BOTs who are living in Turkey but who are not to be Turkish all the time. These women can be Greek, Armenian, Jewish, Kurdish or any immigrant from neighboring countries. Forth, we could not present the distribution of other histologic types such as clear cell and endometrioid cell because they were quite rare in BOTs. Finally, although we mapped the histologic distribution of BOTs, we cannot determine why these geographical differences exist, although they are likely to be a consequence of ethnicity and lifestyle factors. More research
Borderline tumor histology according to geographic region is needed to understand this phenomenon. Despite these limitations, our review is the first to provide evidence on the worldwide histologic distribution of BOTs. While the histologic distribution of BOTs is considerably different in various parts of the world, it appears that specific patterns exist. In general, serous-type BOTs are the predominantly-identified histology in North America, the Middle East, and most of Europe. In contrast, mucinous-type BOTs predominate in East Asia and parts of Europe. The results of this review are important for investigators planning to conduct multi-national clinical trials in patients with BOTs. Without a general understanding of the histologic distribution of BOTs, data reported from one geographic region are difficult to apply to women living in other geographic regions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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