Title: WORLDWIDE COMPARISON OF OVARIAN CANCER SURVIVAL: MORPHOLOGICAL SUBTYPE AND STAGE AT DIAGNOSIS (CONCORD-2)

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ABSTRACT

Objective: Ovarian cancer comprises several subtypes with widely differing levels of survival. We aimed to explore international variation in survival for each subtype to help interpret international differences in survival from all ovarian cancers combined. We also examined differences in stage-specific survival.

Methods: The CONCORD programme is the largest population-based study of global trends in cancer survival, including data from 60 countries for 695,932 women (aged 15-99 years) diagnosed with ovarian cancer during 1995 to 2009. We defined six morphological groups: type I epithelial, type II epithelial, germ cell, sex cord-stromal, other specific non-epithelial and non-specific morphology, and estimated age-standardised 5-year net survival for each country by morphological group. We also analysed data from 64 cancer registries for 233,659 women diagnosed from 2001 to 2009, for whom information on stage at diagnosis was available. We estimated age-standardised 5-year net survival by stage at diagnosis (localised or advanced).

Results: Survival from type I epithelial ovarian tumours for women diagnosed during 2005-09 ranged from 40 to 70%. Survival from type II epithelial tumours was much lower (20-45%). Survival from germ cell tumours was higher than that of type II epithelial tumours, but also varied widely between countries. Survival for sex-cord stromal tumours was higher than for the five other subtypes. Survival from localised tumours was much higher than for advanced disease (80% vs. 30%).

Conclusions: Given the wide variation in survival between morphological groups. Stage at diagnosis remains an important factor in ovarian cancer survival, international comparisons of ovarian cancer survival should incorporate morphology.

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Introduction

The CONCORD-2 study, a comprehensive study on cancer survival, showed wide variation in 5-year net survival for ovarian cancer among over 779,000 women diagnosed in 61 countries(1). Age-standardised survival from ovarian cancer for all morphological subtypes combined was around 30-40% in most countries from 1995 to 2009, but it varied widely between countries. Most international comparisons of ovarian cancer survival include all morphological subtypes combined(1-3). The different morphological groups have unique molecular pathways and treatment, and survival also differs widely, especially for type I and type II epithelial tumours(4-7). We have examined patterns of survival for each distinct morphological group in order to gain a better understanding of international differences in ovarian cancer survival.

Type I epithelial tumours include low-grade serous, endometrioid, clear cell, mucinous and transitional cell (Brenner) carcinomas, while type II epithelial tumours include high-grade serous, undifferentiated carcinoma and malignant mixed mesodermal tumours (carcinosarcoma). Type II epithelial tumours account for approximately 70% of all malignant ovarian tumours, while only 22% of ovarian tumours are type I epithelial. Type I epithelial tumours often present at an early stage and have better prognosis than Type II epithelial tumours, which typically present at an advanced stage(4). Germ cell and sex cord-stromal tumours are rarer types of ovarian cancer, but they generally have much better prognosis than type II epithelial tumours.

Stage at diagnosis also affects survival. Though most women are diagnosed at an advanced stage, stage-specific survival also differs widely between countries(2). In a

comparison of one-year net survival between six high-income countries, Denmark had the highest percentage of women with advanced disease and the second lowest survival for all stages combined(2). Thus, the international variation in ovarian cancer survival may be partially explained by the distribution of stage at diagnosis.

The CONCORD-2 study on the global surveillance of cancer survival has shown the extent to which ovarian cancer survival for all morphological groups combined varies worldwide(1). However, it remains unclear how much of the variation in ovarian cancer survival could be attributed to international variation in survival for each morphological group. We aimed to examine survival from ovarian cancer by morphological group and stage at diagnosis in order to improve understanding of international differences in ovarian cancer survival.

Material and methods

The CONCORD-2 study was based on data for over 25.7 million patients diagnosed with one of 10 cancers, contributed by 279 population-based cancer registries in 67 countries. The data included over 779,000 women diagnosed with ovarian cancer in 61 countries during the 15-year period of 1995 to 2009(1). The CONCORD-2 protocol, ethical approvals and quality control procedures have been described(1).

We analysed data for women (aged 15-99 years) diagnosed during 1995 to 2009 with a cancer of the ovary, fallopian tube, uterine ligaments and adnexa, other specified and unspecified female genital organs, peritoneum and retroperitoneum (International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes C56.9, C57.0-C57.4, C57.7-C57.9, C48.0-C48.2)(8). Recent

evidence suggests that high-grade serous carcinoma, the most common type of ovarian cancer, originates in the fallopian tube. Therefore, cancers of the fallopian tube were included in a broader definition of ovarian cancer(4). Similarly, primary peritoneal malignancies are managed in the same way as advanced-stage epithelial ovarian cancer, and they are also included(4). Tumours of the uterine ligaments and adnexa, other specified and unspecified female genital organs and retroperitoneum were included because of the close proximity of these sites to the ovaries, fallopian tubes and peritoneum. Follow-up until 31 December 2009 for vital status was available. Women diagnosed with ovarian cancer as a second or higher-order primary tumour are included in the analysis, in addition to those for whom ovarian cancer was their first cancer. Women whose cancer registration was from a death certificate or autopsy only were excluded, because their true survival time was unknown.

In ICD-O-2, some borderline tumours were coded as malignant, or with a behaviour code of 3. The behaviour code changed, however, from malignant (behaviour code of 3) to not malignant or of borderline malignancy (behaviour code of 0 or 1) in ICD-O-3. Due to this change in coding, some women diagnosed with borderline tumours were included in the data submissions. ICD-O-3 morphology codes were checked to detect borderline tumours that are now coded with behaviour codes of 0 or 1, and these tumours were then excluded from analysis because their inclusion would inflate survival estimates.

We defined six morphological groups based on ICD-O-3 codes, literature(9) and clinical advice: type I epithelial, type II epithelial, germ cell, sex cord-stromal, other

specific non-epithelial and non-specific morphology [Table 1]. Clear cell, endometrioid, mucinous, squamous and transitional cell (Brenner) carcinomas were classified as type I epithelial. Serous, mixed epithelial-stromal and undifferentiated or other classified epithelial carcinomas were grouped as type II epithelial. Tumours with a non-specific morphology code (8000-8004) were analysed separately. Survival for tumours with unknown morphology (0.1% of cases) is not reported. We included in the analysis all microscopically verified tumours. We also included tumours that were reported as not microscopically verified but for which we had a specific ICD-O-3 morphology code (any valid ICD-O-3 code except 8000-8004).

Information on stage at diagnosis was available only from 2001; therefore, the stage-specific analysis only includes patients diagnosed between 2001 and 2009. Stage at diagnosis was categorised into localised or advanced. Registries submitted stage data coded to one of several classifications: UICC Tumour-Node-Metastasis (TNM) staging system (7th edition), the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) system or SEER Summary Stage 2000. We received data on pathological and/or clinical T, N and M, as well as tumour size (in millimetres) and the number of positive lymph nodes. These data were used to create a final stage at diagnosis variable, prioritising pathological TNM information, supplemented with clinical TNM information where missing. Information on FIGO stage and SEER Summary Stage 2000 was used to supplement missing TNM information when both pathological and clinical TNM were missing, and if no data on tumour size or number of positive lymph nodes were available. TNM Stage I tumours are confined to the ovaries at diagnosis; and were defined as localised in these analyses. Stage II tumours are usually confined to the ovaries, but were defined as advanced in these

analyses. Stage III tumours have spread to regional lymph nodes and Stage IV tumours have metastasised to other organs. TNM Stage III and Stage IV tumours were defined as advanced. Where there was no information available on stage, we classified the tumours as of unknown stage at diagnosis.

We analysed survival by morphological group in each country. We analysed survival by stage at diagnosis in each country, and where possible, for each registry, separately from the analysis by morphological group. Only countries with at least 10 women for a given morphological group for all years combined were included in the analysis for that morphological group. For the stage-specific analysis, we included registries with at least 10 women available for analysis in each stage for any given time period. If more than 30% of tumours were unknown stage at diagnosis for a given registry during 2004-2009, then that registry was excluded from the stage-specific analysis. If fewer than 10 women were available for analysis in a given registry, then the registry was excluded from the analysis by stage at diagnosis. Registries for which net survival estimates were considered as less reliable in the main CONCORD-2 analysis(1) were also excluded. Country-level survival estimates were derived by pooling data for registries that were included in the registry-specific analysis by stage at diagnosis. We only included data from countries that were included in the analysis of specific morphological groups in the analysis for non-specific morphology, given that there were at least 10 women with non-specific tumours available for all years combined. If fewer than 50 women were available for survival analysis by morphological group or stage at diagnosis in a given calendar period, the data for that country were merged.

Net survival is defined as the probability of survival for cancer patients up to a given point in time after diagnosis (for example, 5 years) if death from cancer were to be the only cause of death. Net survival controls for the background mortality of competing causes of death in a population. We used the Pohar Perme estimator of net survival(10), which allows for the fact that competing risks of death increase with age. The Pohar Perme estimator was implemented using *stns*(11) in Stata version 14(12).

Net survival is reported for each country and morphological group, and separately for each registry and each stage at diagnosis. Survival by morphological group was estimated for women diagnosed during 1995-1999, 2000-2004 and 2005-2009. The cohort approach was used for women diagnosed during 1995-1999 and 2000-2004, because five or more years of follow-up were available for all patients, while a period approach was used for 2005-2009. Stage-specific survival was estimated with a cohort approach for 2001-03 and a complete approach was used for 2004-2009.

Survival estimates for all ages combined were age-standardised, where possible, with the International Cancer Standard Survival (ICSS) weights(13). Age at diagnosis was categorised into five age groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. If an age-specific estimate could not be produced, or fewer than 10 women were available for analysis in an age group, data for adjacent age groups were pooled and the re-estimated survival used for both of the original age groups. If two or more age-specific estimates could not be produced, fewer than 10 women were available for analysis in two or more age groups, only the unstandardised estimate is reported.

Results

Data for a total of 695,932 women were available for analysis of survival by morphological group [appendix Figure 1], including 98.3% with a specific morphology, 1.6% with non-specific morphology and 0.1% with unknown morphology [Table 2]. Survival by morphological group was estimated for all stages combined. Most women were diagnosed with Type II epithelial tumours. The mean age at diagnosis varied between morphological subtype, ranging from 36 years for germ cell tumours to 66 years for tumours of non-specific morphology.

Net survival for women diagnosed with type I epithelial tumours five years after diagnosis was fairly high, generally 50-60% [Figure 1]. During 2005 to 2009, age-standardised 5-year survival for type I epithelial tumours varied widely, with the highest survival in Hong Kong (82.9%, 72.4-93.4%) and the lowest in Argentina (30.8%, 16.3-45.2%) [appendix Table 1]. Age-standardised survival from type I epithelial tumours also varied within each continent and over time. The between-country variation in survival was widest in Central and South America (from 30.8%, 16.3-45.2% in Argentina to 77.1%, 64.7-89.6% in Colombia) for women diagnosed during 2004-2009. Age-standardised net survival from type I tumours increased over time in all countries in Central and South America and North America for which data were available. In Asia, Europe, and Oceania, most countries saw an improvement in survival from type I tumours, but survival actually fell over time for some countries in these regions (from 65.5%, 59.0-72.1% to 60.8%, 50.7-70.8% in Korea and from 60.3%, 49.8-70.7% to 56.9%, 42.6-71.3% in Turkey (Izmir)) [appendix Table 1].

Survival from type II epithelial tumours five years after diagnosis was lower than that

of type I epithelial tumours, around only 20-45% [Figure 1]. For women diagnosed between 2005 and 2009, the highest age-standardised survival was seen in Hong Kong (61.5%, 54.8-68.2%), compared with only 18.1% (6.3-29.9%) for women in Chile (Los Rios). Age-standardised survival from type II epithelial tumours increased over time for most countries worldwide, though there were decreases in some countries. In Cuba, for example, survival was 53.4% (45.1-61.7%) for women diagnosed during 1995-99, but only 39.2% (29.3-49.1%) during 2005-2009 [appendix Table 1]. Between-country variation was widest in Central and South America, where age-standardised 5-year survival was only 18.1% (6.3-29.9%) in Chile (Los Rios), but 55.0% (44.6-65.5%) in Ecuador (Quito). Type II epithelial was the only morphological group for which survival estimates could be produced for all five African countries, but all of these estimates were not age standardised.

Survival from germ cell tumours could only be presented for all women diagnosed between 1995 and 2009, because these tumours are so uncommon. As a result, most survival estimates for germ cell tumours were not age standardised. This is because younger women have the highest incidence of germ cell tumours and this subtype is extremely rare in older women. Therefore, only for a few countries were enough women available in each age group to allow for age standardisation. Considering the age-standardised estimates, the highest was in Australia (76.0%, 57.6-94.5%) and the lowest in China (41.5%, 23.6-59.4%) [Figure 2; appendix Table 1].

Sex cord-stromal tumours are also rare, and survival could only be estimated in 11 countries for all three calendar periods. During 2005-2009, net survival was over

90% at 5 years after diagnosis in Korea (100.0%, 96.0-100.0%, n=207 women) and Portugal (94.1%, 83.3-100.0%, n=64 women). However, survival varied widely between countries, and the lowest survival was almost half that seen in Korea (Japan, 58.9%, 34.2-83.7%, n=63 women). Over time, survival from sex cord-stromal tumours remained either stable, or increased, in most countries [Figure 2; appendix Table 1].

Survival from other specific non-epithelial tumours was generally around 40% and slightly higher than that of type II epithelial tumours. The variation in survival was wide, ranging from only 0.3% (0.0-0.8%) in Bulgaria to 60.0% (48.4-71.5%) in Cuba [Figure 2; appendix Table 1].

Age-standardised net survival for tumours of non-specific morphology was generally lower than, that of tumours with specific morphology, with a few notable exceptions [appendix Table 2].

Data for 233,659 women were available from 67 registries in 25 countries for analysis of survival by stage [appendix Figure 2]. Survival by stage at diagnosis was estimated for all ovarian cancer morphologies combined. Only two Central and South American registries provided enough information on stage at diagnosis to be included in the analysis. In North America, one Canadian registry and 36 US registries provided adequate stage data. In Asia and Europe, only 12 and 13 registries, respectively, provided adequate stage data for inclusion in survival analyses. No data from African registries were available for analysis by stage at diagnosis.

Overall, 38,033 (16.3%) of these 233,659 women were diagnosed with localised ovarian cancer, 169,033 (72.3%) with advanced disease and 26,593 (11.4%) with unknown stage at diagnosis. The overall mean age was 64 years. Women diagnosed with localised ovarian cancer were the youngest (mean age 56 years), while women with an unknown stage at diagnosis were the oldest (mean age 68 years). The mean age at diagnoses for women diagnosed with advanced disease was 65 years.

Overall, 5-year age-standardised net survival for localised ovarian cancer (around 80%) was much higher than that for advanced (around 30%) and unknown stages (around 30%) [Figure 3]. For women diagnosed with localised ovarian cancer during 2004-2009, survival was much higher than for women diagnosed with advanced disease everywhere. In some countries, 5-year age-standardised survival was over 90% for localised tumours, with the highest survival in Hong Kong (95.5%, 89.4-100.0%). The lowest age-standardised survival from localised tumours was seen in Mississippi (US) (68.3%, 52.3-84.4%), however, this is still much higher than the highest survival for advanced-stage tumours during the same time period [appendix Table 3].

For advanced-stage ovarian cancer, survival was generally around 30% [Figure 3]. Age-standardised survival from advanced-stage disease diagnosed during 2004 to 2009 was highest in Tochigi, Japan (39.3%, 22.1-56.5%), while the lowest survival was in Manitoba, Canada (15.4%, 9.0-21.7%). The between-registry variation in survival for advanced-stage disease was not as wide as that of localised disease [appendix Table 3].

Survival from tumours of unknown stage at diagnosis was similar to or lower than that of advanced disease in most registries in Central and South America and North America during 2005-2009. For a few registries, survival from tumours of unknown stage was higher than that for advanced disease. In North America, survival from tumours of unknown stage at diagnosis was 43.7% (95% CI: 39.2-48.2) in Texas but only 31.3% (95% CI: 29.6-33.0%) for advanced-stage tumours. In Florida and Mississippi, survival for tumours of unknown stage was higher than that of advanced-stage disease. In contrast to other regions, age-standardised survival from tumours of unknown stage was higher than for advanced stage disease in all Asian, European and Oceanic registries [appendix Table 3].

Discussion

There are few international comparisons of survival for the various morphological subtypes of ovarian cancer. The results from this large study show the importance of morphology in comparisons of survival from ovarian cancer between countries.

The distribution of morphological groups may explain some of the wide international variation in survival. In Asia, for example, type I epithelial tumours are more common than in other regions, is in part due to a higher percentage of clear cell tumours. Because survival for type I epithelial tumours is generally higher than that of type II epithelial tumours, we would expect survival for all morphological groups combined to be higher in Asian countries with this larger proportion of more favourable tumours. As shown in the results, survival for all morphologies combined was generally higher in Asian countries than other regions. It is therefore important to

examine survival from ovarian cancer for each morphological group separately, at least in international comparisons, because survival for all morphologies combined may be influenced by a higher proportion of tumours with a more favourable outcome.

The results also confirm that survival is higher for type I epithelial, germ cell and sex cord-stromal tumours than for the more aggressive type II epithelial tumours. Survival from tumours with a non-specific morphology is also much lower than for tumours in any of these specific morphology groups. We would expect survival from tumours of non-specific morphology to be even lower than that of type II tumours, because most women diagnosed with ovarian cancer for whom a specific morphology is not recorded are likely to have been too sick to undergo surgery, which is required for pathological examination and morphological classification of the tumour. However, tumours recorded as unknown morphology or non-specific morphology, may be recorded as such due to lack of or incomplete pathological information reported to registries.

Survival for localised tumours was much higher than for either advanced tumours or tumours of unknown stage. Early diagnosis of ovarian cancer is thus pathologically important. The result for tumours of unknown stage is not surprising, because accurate staging can only be achieved if a woman has undergone surgery. Women with significantly advanced disease are less likely to have surgery and are therefore less likely to be staged appropriately at diagnosis. Furthermore, women with higher comorbidity, some of whom will also have advanced-stage disease, may not be healthy enough for surgery and may also not have their tumours staged

appropriately.

In some countries, however, survival from tumours of unknown stage was higher than that for advanced-stage tumours. In these countries, it seems more likely that unknown stage at diagnosis may be due to lack of reporting stage to registries or incomplete staging at diagnosis.

Some cancer registries do not routinely collect data on tumour grade, and no information on grade was available for this study. Therefore, some serous tumours may have been misclassified, because grade is required to classify these tumours appropriately. Only high-grade serous tumours are considered as type II epithelial, but we included all serous tumours in our definition of type II epithelial, because grade was not available. We feel confident that the effect on survival is small, because only a small proportion (5%) of serous tumours are of low grade(14).

We have classified all endometrioid tumours as type I epithelial, despite this subtype being previously sub-divided into type I and type II epithelial tumours(4). If grade had been available, only low-grade endometrioid tumours would have been classified as type I epithelial while high-grade endometrioid tumours should have been classified as type II epithelial based on previous definitions of type I and type II epithelial tumours(4). As with low-grade serous tumours, however, high-grade endometrioid tumours are rare, so the inclusion of these tumours in the type I epithelial group should not greatly affect the survival estimate by morphological group(14). An update in 2016 to the classification of endometrioid tumours into type I and type II epithelial tumours now classifies all endometrioid tumours as type I regardless, of tumour

grade(15). A sensitivity analysis was conducted to determine how the survival estimates varied between the two possible classifications for endometrioid tumours. Survival for both type I and type II epithelial increased when endometrioid tumours were included in each group separately. Because survival from endometrioid tumours was generally high when examined separately, we feel confident that including these tumours with the less-aggressive type I epithelial subtypes is preferable.

Tumour stage is not routinely collected by cancer all registries; therefore, the analysis by stage at diagnosis could only include data from 25 countries. Additionally, changes in coding of stage at diagnosis in the US (72.7% of women included in the analysis) from the Summary Staging Guide 1977 to SEER Summary Stage 2000 meant that only data from 2001 forward could be included from the US.

The quality and comparability of morphology data between countries may be limited due to differences in diagnostic techniques, morphological classification and transfer of data to the cancer registry. Almost all tumours submitted by Sweden were type II epithelial, the majority of which were unspecific epithelial carcinomas. Given that previous studies show a wider distribution of morphological subtypes(16), it is unlikely that almost all tumours from Sweden included in our analysis would have been true type II epithelial tumours. Additionally, Hong Kong only submitted epithelial ovarian cancers when submitting data for the CONCORD-2 study. Therefore, the survival comparison is limited to type I and type II epithelial tumours for Hong Kong.

Our analysis was limited to tumours that had been reported by the registry as

morphologically verified, though we also included tumours with specific ICD-O-3 morphology codes regardless of the reported basis of diagnosis. Morphological verification requires a tumour biopsy, thus, may not be performed if the woman presents with advanced-stage disease and is older or has a high number of comorbidities. Additionally, morphological verification may be difficult in low resource settings, where survival may be lower. Therefore, limiting our analysis to morphologically verified tumours may overestimate survival. However, given that 92.7% of tumours were morphologically verified, the bias would be small.

Data on treatment are not routinely collected by all cancer registries, and the registries included in the CONCORD programme were not asked to submit data on treatment. Therefore, we were unable to evaluate the impact of treatment, or lack thereof, on survival estimates for each morphological group or stage at diagnosis.

The method of follow-up for obtaining the vital status of registered patients varied between cancer registries. Around 60% of registries reported using only passive follow-up, 2% reported only using active follow-up and 38% reported using both methods. The majority of patients were followed until death or at least five years after diagnosis. The data for this analysis come from the main CONCORD-2 data (n=779,302), in which only 0.6% of women were lost to follow-up and only 0.6% were censored, or diagnosed from 1995-2004 and a vital status of “alive”, but with less than five years of follow-up(1).

This is the largest international population-based study of survival for ovarian cancer by morphological subtype and stage at diagnosis. The large number of women

included allowed for comparison of survival from epithelial and non-epithelial tumours, which are usually studied separately, complicating comparisons of survival between populations or over time. The differences in survival between the morphological groups emphasise the need to focus future international comparisons of ovarian cancer survival on the various subtypes, rather than analysing ovarian cancer as a single homogenous group. The results from this analysis also emphasise the need for further development of high-quality population-based cancer registries in low-income countries, and the continued improvement of the quality and completeness of cancer registry data in all countries.

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Conflict of Interest

The authors declare there are no conflicts of interest.

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Table 1. Ovarian cancer morphological groups and subtypes[a]

[a] No information on grade was available, therefore all endometrioid tumours were classified as type I epithelial.
[b] No information on grade was available, therefore all serous tumours were classified as type II epithelial
[c] Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) were excluded from the analysis of distribution of morphological subtypes (see text).

Table 2. Worldwide distribution of morphology and mean age at diagnosis, 1995-2009

[a] Standard deviation.
[b] No information on grade was available, therefore all endometrioid tumours were classified as type I epithelial.
[c] No information on grade was available, therefore all serous tumours were classified as type II epithelial.

Supplementary Table 1. Five-year age-standardised net survival (95% CI) by country[a], period of diagnosis and morphological group[b]

Italics denote net survival estimates that are not age-standardised.
Where two or more calendar periods of diagnosis were merged, the net survival estimates are underlined.
[a] Countries with fewer than 10 women for any morphological group (all calendar periods combined) were not included in the analysis.
[b] Only microscopically verified tumours or tumours with a clinical diagnosis but speific mophology code are included.
[c] Endometrioid tumours are defined as type I epithelial.
[d] Serous tumours are defined as type II epithelial.
[e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The number of patients in each time period may differ from Table 4 due to merging of calendar periods.

Supplementary Table 2. Five-year age-standardised net survival (95% CI) by country[a], period of diagnosis for all tumours, tumours of known morphology[b] and tumours of unknown morphology[b]

Italics denote net survival estimates that are not age-standardised.
Where two or more calendar periods of diagnosis were merged, the net survival estimates are underlined.
[a] Countries with fewer than 10 women for any morphological group (all calendar periods combined) were not included in the analysis.
[b] Only microscopically verified tumours or tumours with a clinical diagnosis but speific mophology code are included.
[c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of

759 borderline tumours and updates from registries. The number of patients in each time period
760 may differ from Table 3 due to merging of calendar periods.
761
762
763 **Supplementary Table 3.** Five-year age-standardised net survival (95% CI) by
764 continent, country, registry[a] calendar period and stage at diagnosis
765
766 Italics denote net survival estimates that are not age-standardised.
767 Where two or more calendar periods of diagnosis were merged, the net survival estimates
768 are underlined.
769 [a] Registries with fewer than 10 women for any stage (all calendar period combined) were not
770 included in the analysis.
771 [b] Number of patients included in analysis for a given calendar period. The number of women
772 per registry may differ from the main CONCORD-2 analysis due to the exclusion of
773 borderline tumours and updates from registries. The total number for a country in a given
774 calendar period may not equal the sum of the number per registry for that period due to
775 merging of calendar periods to produce the registry level estimates.
776

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