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

3

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19 **ABSTRACT**

20

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

25

26 **Methods:** The CONCORD programme is the largest population-based study of
27 global trends in cancer survival, including data from 60 countries for 695,932 women
28 (aged 15-99 years) diagnosed with ovarian cancer during 1995 to 2009. We defined
29 six morphological groups: type I epithelial, type II epithelial, germ cell, sex cord-
30 stromal, other specific non-epithelial and non-specific morphology, and estimated
31 age-standardised 5-year net survival for each country by morphological group. We
32 also analysed data from 64 cancer registries for 233,659 women diagnosed from
33 2001 to 2009, for whom information on stage at diagnosis was available. We
34 estimated age-standardised 5-year net survival by stage at diagnosis (localised or
35 advanced).

36

37 **Results:** Survival from type I epithelial ovarian tumours for women diagnosed during
38 2005-09 ranged from 40 to 70%. Survival from type II epithelial tumours was much
39 lower (20-45%). Survival from germ cell tumours was higher than that of type II
40 epithelial tumours, but also varied widely between countries. Survival for sex-cord
41 stromal tumours was higher than for the five other subtypes. Survival from localised
42 tumours was much higher than for advanced disease (80% vs. 30%).

43

44 **Conclusions:** Given the wide variation in survival between morphological groups.

45 Stage at diagnosis remains an important factor in ovarian cancer survival,

46 international comparisons of ovarian cancer survival should incorporate morphology.

47

48 Word count: 248

49 **Introduction**

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

60

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

71

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

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

78

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

86

87 **Material and methods**

88 The CONCORD-2 study was based on data for over 25.7 million patients diagnosed
89 with one of 10 cancers, contributed by 279 population-based cancer registries in 67
90 countries. The data included over 779,000 women diagnosed with ovarian cancer in
91 61 countries during the 15-year period of 1995 to 2009(1). The CONCORD-2
92 protocol, ethical approvals and quality control procedures have been described(1).

93

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

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

112
113 In ICD-O-2, some borderline tumours were coded as malignant, or with a behaviour
114 code of 3. The behaviour code changed, however, from malignant (behaviour code
115 of 3) to not malignant or of borderline malignancy (behaviour code of 0 or 1) in ICD-
116 O-3. Due to this change in coding, some women diagnosed with borderline tumours
117 were included in the data submissions. ICD-O-3 morphology codes were checked to
118 detect borderline tumours that are now coded with behaviour codes of 0 or 1, and
119 these tumours were then excluded from analysis because their inclusion would
120 inflate survival estimates.

121
122 We defined six morphological groups based on ICD-O-3 codes, literature(9) and
123 clinical advice: type I epithelial, type II epithelial, germ cell, sex cord-stromal, other

124 specific non-epithelial and non-specific morphology [Table 1]. Clear cell,
125 endometrioid, mucinous, squamous and transitional cell (Brenner) carcinomas were
126 classified as type I epithelial. Serous, mixed epithelial-stromal and undifferentiated or
127 other classified epithelial carcinomas were grouped as type II epithelial. Tumours
128 with a non-specific morphology code (8000-8004) were analysed separately.

129 Survival for tumours with unknown morphology (0.1% of cases) is not reported. We
130 included in the analysis all microscopically verified tumours. We also included
131 tumours that were reported as not microscopically verified but for which we had a
132 specific ICD-O-3 morphology code (any valid ICD-O-3 code except 8000-8004).

133

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

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

153

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

173

174 Net survival is defined as the probability of survival for cancer patients up to a given
175 point in time after diagnosis (for example, 5 years) if death from cancer were to be
176 the only cause of death. Net survival controls for the background mortality of
177 competing causes of death in a population. We used the Pohar Perme estimator of
178 net survival(10), which allows for the fact that competing risks of death increase with
179 age. The Pohar Perme estimator was implemented using *stns*(11) in Stata version
180 14(12).

181

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

189

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

198

199 **Results**

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

207

208 Net survival for women diagnosed with type I epithelial tumours five years after
209 diagnosis was fairly high, generally 50-60% [Figure 1]. During 2005 to 2009, age-
210 standardised 5-year survival for type I epithelial tumours varied widely, with the
211 highest survival in Hong Kong (82.9%, 72.4-93.4%) and the lowest in Argentina
212 (30.8%, 16.3-45.2%) [appendix Table 1]. Age-standardised survival from type I
213 epithelial tumours also varied within each continent and over time. The between-
214 country variation in survival was widest in Central and South America (from 30.8%,
215 16.3-45.2% in Argentina to 77.1%, 64.7-89.6% in Colombia) for women diagnosed
216 during 2004-2009. Age-standardised net survival from type I tumours increased over
217 time in all countries in Central and South America and North America for which data
218 were available. In Asia, Europe, and Oceania, most countries saw an improvement
219 in survival from type I tumours, but survival actually fell over time for some countries
220 in these regions (from 65.5%, 59.0-72.1% to 60.8%, 50.7-70.8% in Korea and from
221 60.3%, 49.8-70.7% to 56.9%, 42.6-71.3% in Turkey (Izmir)) [appendix Table 1].

222

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

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

236

237 Survival from germ cell tumours could only be presented for all women diagnosed
238 between 1995 and 2009, because these tumours are so uncommon. As a result,
239 most survival estimates for germ cell tumours were not age standardised. This is
240 because younger women have the highest incidence of germ cell tumours and this
241 subtype is extremely rare in older women. Therefore, only for a few countries were
242 enough women available in each age group to allow for age standardisation.

243 Considering the age-standardised estimates, the highest was in Australia (76.0%,
244 57.6-94.5%) and the lowest in China (41.5%, 23.6-59.4%) [Figure 2; appendix Table
245 1].

246

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

249 90% at 5 years after diagnosis in Korea (100.0%, 96.0-100.0%, n=207 women) and
250 Portugal (94.1%, 83.3-100.0%, n=64 women). However, survival varied widely
251 between countries, and the lowest survival was almost half that seen in Korea
252 (Japan, 58.9%, 34.2-83.7%, n=63 women). Over time, survival from sex cord-stromal
253 tumours remained either stable, or increased, in most countries [Figure 2; appendix
254 Table 1].

255

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

260

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

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

273

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

281

282 Overall, 5-year age-standardised net survival for localised ovarian cancer (around
283 80%) was much higher than that for advanced (around 30%) and unknown stages
284 (around 30%) [Figure 3]. For women diagnosed with localised ovarian cancer during
285 2004-2009, survival was much higher than for women diagnosed with advanced
286 disease everywhere. In some countries, 5-year age-standardised survival was over
287 90% for localised tumours, with the highest survival in Hong Kong (95.5%, 89.4-
288 100.0%). The lowest age-standardised survival from localised tumours was seen in
289 Mississippi (US) (68.3%, 52.3-84.4%), however, this is still much higher than the
290 highest survival for advanced-stage tumours during the same time period [appendix
291 Table 3].

292

293 For advanced-stage ovarian cancer, survival was generally around 30% [Figure 3].
294 Age-standardised survival from advanced-stage disease diagnosed during 2004 to
295 2009 was highest in Tochigi, Japan (39.3%, 22.1-56.5%), while the lowest survival
296 was in Manitoba, Canada (15.4%, 9.0-21.7%). The between-registry variation in
297 survival for advanced-stage disease was not as wide as that of localised disease
298 [appendix Table 3].

299

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

310

311 **Discussion**

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

315

316 The distribution of morphological groups may explain some of the wide international
317 variation in survival. In Asia, for example, type I epithelial tumours are more common
318 than in other regions, is in part due to a higher percentage of clear cell tumours.

319 Because survival for type I epithelial tumours is generally higher than that of type II
320 epithelial tumours, we would expect survival for all morphological groups combined
321 to be higher in Asian countries with this larger proportion of more favourable
322 tumours. As shown in the results, survival for all morphologies combined was
323 generally higher in Asian countries than other regions. It is therefore important to

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

328

329 The results also confirm that survival is higher for type I epithelial, germ cell and sex
330 cord-stromal tumours than for the more aggressive type II epithelial tumours.

331 Survival from tumours with a non-specific morphology is also much lower than for
332 tumours in any of these specific morphology groups. We would expect survival from
333 tumours of non-specific morphology to be even lower than that of type II tumours,
334 because most women diagnosed with ovarian cancer for whom a specific
335 morphology is not recorded are likely to have been too sick to undergo surgery,
336 which is required for pathological examination and morphological classification of the
337 tumour. However, tumours recorded as unknown morphology or non-specific
338 morphology, may be recorded as such due to lack of or incomplete pathological
339 information reported to registries.

340

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

349 appropriately.

350

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

355

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

363

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

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

381

382 Tumour stage is not routinely collected by cancer all registries; therefore, the
383 analysis by stage at diagnosis could only include data from 25 countries.

384 Additionally, changes in coding of stage at diagnosis in the US (72.7% of women
385 included in the analysis) from the Summary Staging Guide 1977 to SEER Summary
386 Stage 2000 meant that only data from 2001 forward could be included from the US.

387

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

397

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

399 morphologically verified, though we also included tumours with specific ICD-O-3
400 morphology codes regardless of the reported basis of diagnosis. Morphological
401 verification requires a tumour biopsy, thus, may not be performed if the woman
402 presents with advanced-stage disease and is older or has a high number of
403 comorbidities. Additionally, morphological verification may be difficult in low resource
404 settings, where survival may be lower. Therefore, limiting our analysis to
405 morphologically verified tumours may overestimate survival. However, given that
406 92.7% of tumours were morphologically verified, the bias would be small.

407

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

412

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

421

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

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

433

434 Word count: 3984

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669 **Conflict of Interest**

670 The authors declare there are no conflicts of interest.

671 **References**

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709

710 **List of tables**711 **Table 1.** Ovarian cancer morphological groups and subtypes^a712 ^a No information on grade was available, therefore all endometrioid tumours were
713 classified as type I epithelial.714 ^b No information on grade was available, therefore all serous tumours were classified
715 as type II epithelial716 ^c Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473)
717 were excluded from the analysis of distribution of morphological subtypes (see text).
718719 **Table 2.** Worldwide distribution of morphology and mean age at diagnosis, 1995-
720 2009721 ^a Standard deviation.722 ^b No information on grade was available, therefore all endometrioid tumours were
723 classified as type I epithelial.724 ^c No information on grade was available, therefore all serous tumours were classified
725 as type II epithelial.
726727 **Supplementary Table 1.** Five-year age-standardised net survival (95% CI) by
728 country^a, period of diagnosis and morphological group^b

729

730 *Italics denote net survival estimates that are not age-standardised.*731 *Where two or more calendar periods of diagnosis were merged, the net survival estimates*
732 *are underlined.*733 ^a Countries with fewer than 10 women for any morphological group (all calendar periods
734 combined) were not included in the analysis.735 ^b Only microscopically verified tumours or tumours with a clinical diagnosis but specific
736 morphology code are included.737 ^c Endometrioid tumours are defined as type I epithelial.738 ^d Serous tumours are defined as type II epithelial.739 ^e Number of patients included in the analysis for a given calendar period. The number of
740 women per registry may differ from the main CONCORD-2 analysis due to the exclusion of
741 borderline tumours and updates from registries. The number of patients in each time period
742 may differ from Table 4 due to merging of calendar periods.
743

744

745

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

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750

751 *Italics denote net survival estimates that are not age-standardised.*752 *Where two or more calendar periods of diagnosis were merged, the net survival estimates*
753 *are underlined.*754 ^a Countries with fewer than 10 women for any morphological group (all calendar periods
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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.

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780 ovarian tumours by country, 2005-2009

781 *Data with 100% coverage of the national population.

782 † Estimate not age-standardised.

783 ‡ Data for two or more calendar periods of diagnosis have been merged.

784 95% CI represented by error bars. Ranked from highest to lowest net survival by
785 continent for women diagnosed in the calendar period of 2005-2009.

786

787 **Figure 2.** 5-year age-standardised net survival for germ cell, sex cord-stromal and
788 other specific non-epithelial ovarian tumours by country, 2005-2009

789 *Data with 100% coverage of the national population.

790 † Estimate not age-standardised.

791 ‡ Data for two or more calendar periods of diagnosis have been merged.

792 95% CI represented by error bars. Ranked from highest to lowest net survival by
793 continent for women diagnosed in the calendar period of 2005-2009.

794 **Figure 3.** 5-year age-standardised net survival for localised-stage and advanced-
795 stage ovarian tumours by country, 2004-2009

796 † Estimate not age-standardised.

797 ‡ Data for 2001-2003 and 2004-2009 have been merged.

798 95% CI represented by error bars.

799 **Supplementary Figure 1.** Flow chat of data exclusions for analysis by morphological
800 group

801 **Supplementary Figure 2.** Flow chat of data exclusions for analysis by stage at
802 diagnosis

803