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Matz, M; Coleman, MP; Sant, M; Chirlaque, MD; Visser, O; Gore, M; Allemani, C; & the CONCORD Working Group, (2016) The histology of ovarian cancer: worldwide distribution and implications for international survival comparisons (CONCORD-2). *Gynecologic oncology*. ISSN 0090-8258 DOI: <https://doi.org/10.1016/j.ygyno.2016.10.019>

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DOI: [10.1016/j.ygyno.2016.10.019](https://doi.org/10.1016/j.ygyno.2016.10.019)

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1 **Title: THE MORPHOLOGY OF OVARIAN CANCER: WORLDWIDE**
2 **DISTRIBUTION AND IMPLICATIONS FOR INTERNATIONAL SURVIVAL**
3 **COMPARISONS (CONCORD-2)**

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26 **ABSTRACT**

27 **Objective:** Ovarian cancers comprise several morphologically distinct tumour
28 groups with widely different prognosis. We aimed to describe the worldwide
29 distribution of ovarian cancer morphology and to understand what role this
30 may play in international variation in survival.

31

32 **Methods:** The CONCORD programme is the largest population-based study
33 of global trends in cancer survival. Data on 681,759 women diagnosed during
34 1995-2009 with cancer of the ovary, fallopian tube, peritoneum and
35 retroperitoneum in 51 countries were included. We categorised ovarian
36 tumours into six morphological groups, and explored the worldwide
37 distribution of morphology.

38

39 **Results:** During 2005-2009, type II epithelial tumours were the most common.
40 The proportion was much higher in Oceania (73.1%), North America (73.0%)
41 and Europe (72.6%) than in Central and South America (65.7%) and Asia
42 (56.1%). By contrast, type I epithelial tumours were more common in Asia
43 (32.5%), compared with only 19.4% in North America. From 1995 to 2009, the
44 proportion of type II epithelial tumours increased from 68.6% to 71.1%, while
45 the proportion of type I epithelial tumours fell from 23.8% to 21.2%. The
46 proportions of germ cell tumours, sex cord-stromal tumours, other specific
47 non-epithelial tumours and tumours of non-specific morphology all remained
48 stable over time.

49

50 **Conclusions:** The distribution of ovarian cancer morphology varies widely

51 worldwide. Type I epithelial, germ cell and sex cord-stromal tumours are
52 generally associated with higher survival than type II tumours, so the
53 proportion of these tumours may influence survival estimates for all ovarian
54 cancers combined. The distribution of morphological groups should be
55 considered when comparing survival between countries and regions.

56

57 Word count: 250

58 **Introduction**

59 Of all gynaecological malignancies, ovarian cancer causes the second highest
60 number of deaths worldwide, accounting for over 151,000 deaths annually(1).

61 Symptoms, such as persistent abdominal pain, bloating or decreased
62 appetite, are vague(2). Most women present with advanced-stage disease(3)
63 and five-year survival is around 30-40%(4). Ovarian cancer is not a single
64 disease(2, 5), but includes several morphological subtypes that have widely
65 different prognosis(6, 7).

66

67 Ovarian cancer has been divided into epithelial and non-epithelial groups for
68 many years, but recent work has enabled finer subdivision of epithelial ovarian
69 cancers into different groups according to a combination of morphological and
70 clinical characteristics(6-10). Type I epithelial tumours include low-grade
71 serous, endometrioid, clear cell, mucinous and transitional cell (Brenner)
72 carcinomas. They often present at an early stage, may arise from borderline
73 ovarian tumours or endometriosis and typically have a good prognosis. Type II
74 epithelial tumours comprise high-grade serous carcinoma, undifferentiated
75 carcinomas and malignant mixed mesodermal tumours. They account for
76 around 75% of epithelial ovarian cancers, typically present at an advanced
77 stage and have a poor prognosis(6, 7, 9). Each morphological group has
78 distinct molecular pathways that influence chemosensitivity, the pattern of
79 metastasis and the probability of survival(9, 11).

80

81 The pathogenesis of ovarian cancer is not fully understood. Recent evidence,
82 particularly from prophylactic oophorectomies in women at a high risk of

83 ovarian cancer because of BRCA gene mutations, suggests that the most
84 common subtype, high-grade serous carcinoma, originates either in the
85 fallopian tube or on the surface of the ovary. Therefore, fallopian tube
86 carcinoma has more recently been included in a broader definition of ovarian
87 cancer(7). Primary peritoneal carcinoma is also managed in the same way as
88 advanced-stage epithelial ovarian cancer(6, 12).

89

90 International comparisons of cancer incidence, mortality and survival are
91 crucial to inform and plan health policy and cancer control programmes. Low
92 survival has been a stimulus for cancer plans and strategies in many
93 countries, such as the United Kingdom and Denmark(3). Comparisons of lung
94 cancer survival have routinely been divided into small-cell and non-small cell
95 subtypes due to the different prognosis and behaviour of these tumours.

96 Ovarian cancer is arguably an even more heterogeneous disease than lung
97 cancer, and morphology should thus be considered in the interpretation of
98 international variation in ovarian cancer survival. Type I epithelial tumours are
99 generally associated with higher survival than type II tumours, so the
100 proportion of type I epithelial tumours may influence survival estimates for all
101 ovarian cancers combined. Differences in the distribution of morphology may
102 thus contribute to international variations in survival from all ovarian cancers
103 combined, in addition to international differences in stage at diagnosis and
104 treatment.

105

106 The CONCORD-2 study on the global surveillance of cancer survival has
107 shown the extent to which ovarian cancer survival varies worldwide(4).

108 However, it remains unclear how much of the variation in ovarian cancer
109 survival could be attributed to international variation in the morphological
110 subtypes, in particular the distribution of type I and type II epithelial tumours.
111 Using population-based data from the CONCORD-2 study, we have examined
112 the international distribution of ovarian cancer morphology. Our aims were to
113 describe the worldwide variation of ovarian cancer morphological groups, and
114 then to discuss whether this variation may influence international comparisons
115 of population-based cancer survival.

116

117 **Methods**

118 The CONCORD-2 study(4) collected information for over 779,000 adult
119 women (aged 15-99 years) in 61 countries who were diagnosed during the 15-
120 year period 1995-2009 with a cancer of the ovary, fallopian tube, uterine
121 ligaments and adnexa, other specific and unspecified female genital organs,
122 peritoneum or retroperitoneum (International Classification of Diseases for
123 Oncology, 3rd edition (ICD-O-3) topography codes C56.9, C57.0-C57.4,
124 C57.7-C57.9, C48.0-C48.2)(13). The CONCORD-2 protocol, the ethical
125 approvals and the quality control procedures have been described(4).

126

127 We defined six morphological groups based on previous literature(14) and
128 clinical advice [Table 1]. Clear cell, endometrioid, mucinous, squamous and
129 transitional cell carcinomas were grouped as type I epithelial tumours, and
130 serous carcinoma, mixed epithelial and stromal carcinoma and
131 undifferentiated and other epithelial carcinoma were grouped as type II
132 epithelial tumours.

133

134 Ovarian cystadenomas were reclassified in ICD-O-3 from invasive (behaviour
135 code of 3) to borderline (behaviour code of 0 or 1), but some registries coded
136 tumours of borderline behaviour as invasive despite the changes from ICD-O-
137 2 to ICD-O-3. Borderline tumours were excluded from the analysis of the
138 distribution. Morphology codes for haematological malignancies were also
139 excluded from analysis.

140

141 Data were available for 793,098 women for analysis [supplementary Figure 1].
142 Women diagnosed with borderline tumours, haematological malignancies or
143 whose records included invalid ICD-O-3 codes (codes not included in either
144 ICD-O-2 or ICD-O-3) were excluded (n=13,073). Of the remaining 780,025
145 women, 90.6% (706,807) had tumours that were coded by the registry as
146 having been morphologically verified, while 7.5% (58,682) were coded as not
147 morphologically verified and 1.9% (14,536) were coded as unknown whether
148 morphologically verified or not. For tumours coded as morphologically verified,
149 705,997 (99.9%) had a valid ICD-O-3 morphology code, but no morphology
150 code was available for 810 (0.1%), and these tumours were excluded.
151 Tumours coded as not morphologically verified were primarily tumours of
152 unknown morphology (30,287, 51.6% of non-morphologically verified
153 tumours); these tumours were excluded. We excluded a further 18,200 non-
154 morphologically verified tumours with non-specific morphology. We included
155 the remaining 10,195 tumours that had been coded as not having been
156 morphologically verified, because a specific ICD-O-3 morphology code was
157 nevertheless available, implying that morphological verification had in fact

158 been performed. Tumours for which it was unknown whether morphological
159 verification had been performed or not were evenly distributed across specific
160 (n=5,017), non-specific (n=4,798) and unknown morphology (n=4,721). Of
161 these tumours, we excluded non-specific and unknown tumours. We included
162 the remaining 5,017 tumours coded as unknown whether morphologically
163 verified, because a specific morphology was also recorded, again implying
164 that morphological verification had been completed.

165

166 In total, 721,209 women (98.3% with specific ICD-O-3 morphology codes and
167 1.7% with non-specific codes) were available for analysis after the first round
168 of exclusions.

169

170 We examined the distribution of ovarian cancer morphology for all countries in
171 any calendar period (1995-1999, 2000-2004 and 2005-2009) for which data
172 were available for at least 100 women. Registries from which the survival
173 estimates in the main CONCORD-2 analysis were considered less reliable(4)
174 were also excluded, because the results from this analysis will be used to
175 inform the results of survival analyses of ovarian cancer. Survival estimates
176 were flagged as less reliable if a higher than usual proportion of patients was
177 excluded from analyses because the cancer was registered only through a
178 death certificate, or the date of last vital status was not known. The focus of
179 this analysis was the distribution of specific morphological groups, so women
180 diagnosed in Sweden had to be excluded, because 97.5% of tumours were
181 coded by the registry as undifferentiated or other epithelial carcinoma or as
182 non-specific morphology (ICD-O-3 codes 8000-8004). After all exclusions,

183 681,759 women (86.0% of the total number for whose data were available for
184 analysis) were included in the analysis of the morphological distribution
185 (192,080 in 1995-1999; 240,397 in 2000-2004; 249,282 in 2005-2009)
186 [supplementary Table 1].

187

188 **Results**

189 Type II epithelial tumours were the most common morphology worldwide
190 (476,461; 69.9%), followed by type I epithelial (152,874; 22.4%) [Figure 1].
191 Germ cell, sex cord-stromal, other specific non-epithelial and non-specific
192 tumours were all rare and they only comprised 8% of tumours worldwide; the
193 distribution of these groups remained relatively stable over the 15-year period
194 1995 to 2009. The proportion of type II epithelial tumours increased slightly
195 from 68.6% to 71.1% from 1995 to 2009, and there was a corresponding
196 decrease in type I epithelial tumours (from 23.8% to 21.2%: supplementary
197 Table 1).

198 During 2005-2009, type II epithelial was the most common group in all
199 continents, although the proportion was much higher in Oceania (73.1%),
200 North America (73.0%) and Europe (72.6%) than in Central and South
201 America (65.7%) and Asia (56.1%) [Table 2]. The range at the national level,
202 however, was much wider. The highest proportion of type II tumours was in
203 Latvia (78.9%), with the lowest proportion in Thailand (40.4%) [supplementary
204 Table 4]. There was little between-country variation in the proportion of type II
205 tumours in Central and South America, North America and Oceania. However,
206 the proportion varied widely in Asia, where the proportion of type II tumours
207 was lower than that of type I epithelial tumours in Hong Kong and Thailand

208 [Figure 3]. There was also variation in the proportion of type II tumours in
209 Europe, where they accounted for over 70% of tumours in 15 countries, 60%
210 in 11 countries and only 50.2% in Russia [supplementary Table 4]. The
211 distribution of type II epithelial subtypes (serous, undifferentiated and other
212 epithelial and mixed epithelial and stromal carcinoma) also varied by country,
213 continent and calendar period [supplementary Table 2, supplementary Table 3
214 and supplementary Table 5].

215

216 Type I epithelial tumours were the second most common group for all
217 continents during 2005-2009, but the range was wide. The highest proportion
218 was seen in Asia (32.5%), while North America showed the lowest proportion
219 (19.4%) [Table 2]. The proportion was similar in all countries in Central and
220 South America, North America and Oceania [supplementary Table 4]. In
221 Europe, however, there was wider variation, the proportion ranging from
222 11.3% in Latvia to 28.7% in Finland [supplementary Table 4]. The variation
223 was even wider for countries in Asia, with the lowest proportion in Israel
224 (12.8%) and the highest in Hong Kong (51.7%) [Figure 3]. The distribution of
225 specific type I epithelial subtypes (clear cell, endometrioid, mucinous,
226 squamous and transitional cell (Brenner)) also varied over time and differed
227 by country and continent [supplementary Table 2, supplementary Table 3 and
228 supplementary Table 5].

229

230 Germ cell tumours were uncommon everywhere; the proportion in Asia (4.2%)
231 was the highest in any continent, over three times the proportion seen in
232 Europe (1.3%) [Table 2]. The proportion was similar for all countries in Europe

233 (1.3%), North America (2.0%) and Oceania (2.5%). However, there was wide
234 variation between countries in Central and South America and Asia. In Central
235 and South America, the lowest proportion (1.6%) was seen in Cuba, and the
236 highest (7.8%) in Ecuador [supplementary Table 4]. Among Asian countries,
237 the variation was wider, with the lowest proportion in Cyprus (0.9%), and the
238 highest in Jordan (8.1%) [Figure 3].

239

240 Sex cord-stromal tumours were even more uncommon than germ cell
241 tumours. The proportion also varied widely between countries in Asia, Central
242 and South America and Europe. The proportion was similar for all countries in
243 North America (1.5%) and Oceania (0.9%) [Table 2, supplementary Table 4].
244 The widest between-country variation was seen in Europe, with only 0.3% of
245 tumours diagnosed as sex cord-stromal in Denmark, but 11.4% in Russia
246 [supplementary Table 4]. In Central and South America, the proportion ranged
247 from 1.6% in Brazil and Puerto Rico to 4.5% in Cuba. The lowest proportion in
248 Asia was in Israel (0.6%), while the highest proportion was in Jordan (4.7%)
249 [Figure 3].

250

251 The highest proportion of other specific non-epithelial tumours (3.4%) was in
252 Central and South America. The proportion was generally less than 5% in all
253 countries, and between-country variation within each continent was small. The
254 widest variation in the proportions was seen in Asia (0.5% in Indonesia and
255 5.8% in Cyprus) and Europe (0.6% in Croatia and 5.9% in Iceland)
256 [supplementary Table 4].

257

258 Non-specific tumours generally accounted for 3% or less of ovarian tumours in
259 all countries. The highest proportion was recorded in Russia (17.7%), much
260 higher than the next highest proportion (Malta, 6.3%). The lowest proportions
261 of non-specific tumours were seen in the Netherlands and Slovenia (0.1%)
262 [supplementary Table 4].

263

264 **Discussion**

265 This is the largest study of the distribution of ovarian cancer morphology. It is
266 based on individual patient records from 218 population-based cancer
267 registries in 51 countries. Data were available for 681,759 women, including
268 249,282 diagnosed between 2005 and 2009. Type II epithelial tumours were
269 the most common morphological group in each continent, but the distribution
270 of morphological groups varied greatly worldwide. The distribution was similar
271 in Europe, North America and Oceania, while there was a much higher
272 proportion of type I epithelial tumours seen in Asia and Central and South
273 America.

274

275 Previous studies of the morphological subtypes of ovarian cancer have
276 focused on epithelial tumours, and they have generally been limited to a small
277 number of countries. One meta-analysis included data for 98,099 women from
278 41 studies published between 1992 and 2012, only 12 of which used data
279 from population-based registries(15). The results were similar to those found
280 in this study, with type II epithelial tumours more common than type I epithelial
281 tumours. The distribution of subtypes between countries included in the meta-
282 analysis was heterogeneous.

283

284 Some of the variations in the distribution of ovarian cancer morphology may
285 be explained by ethnicity. A higher proportion of type II epithelial tumours
286 diagnosed between 2005 and 2009 was reported in Israel (77.8%) than in
287 most other countries. This may be attributable to the fact that a high
288 percentage of the population in Israel is of Jewish ancestry, in whom BRCA1
289 and BRCA2 gene mutations are more common than in other populations.
290 Serous tumours, which are classified as type II epithelial, are the most
291 common morphological subtype among women with BRCA1 and BRCA2
292 mutations(16).

293

294 The proportions of type I and type II epithelial tumours were markedly different
295 between the US and Japan. In Japan, 41.3% of tumours were type I epithelial
296 and 47.5% were type II epithelial, compared to 19.0% and 73.2% in the US
297 [supplementary Table 4]. The lower proportion of serous tumours in Japan
298 and other East Asian countries is due in part to the higher proportion of clear
299 cell cancers [supplementary Table 5]. These differences are most probably
300 due to the higher incidence of endometriosis, a potential pre-cursor of clear
301 cell and endometrioid tumours(17), in East Asian women(18).

302

303 The proportion of mucinous tumours varied, ranging from over 10% in most
304 Asian countries to 5-6% in most North American, European and Oceanian
305 countries. The higher proportion in Japan is not clearly explained. Many
306 tumours classified as mucinous may in fact be metastatic to the ovary from
307 the gastrointestinal tract, including the stomach, which has a high incidence in
308 Asia(19, 20). The reduction in the worldwide proportion of mucinous ovarian

309 cancer from 9.2% to 6.8% between 1995-1999 and 2005-2009
310 [supplementary Table 5] may be partially attributable to more accurate
311 immunohistochemical and imaging assessment, which allows for the
312 exclusion of primary mucinous tumours from a different primary site,
313 particularly those of the gastrointestinal tract. It can otherwise be difficult to
314 differentiate a true primary mucinous ovarian cancer from mucinous tumours
315 that are metastatic to the ovary(21).

316

317 Germ cell and sex cord-stromal tumours of the ovary should be considered
318 separately in survival analysis, because they typically have higher survival
319 than epithelial ovarian cancers. The proportion of germ cell tumours was less
320 than 3% in most countries, but in some Asian and Central and South
321 American countries, the proportions were much higher (5-8%). These
322 differences are important, because the incidence of germ cell tumours is
323 highest among young women and survival is usually very high, even with the
324 tumour is diagnosed at an advanced stage, if optimal treatment is
325 achievable(22). The higher proportion of germ cell tumours in Asia and
326 Central and South America may therefore be due to the younger age profile of
327 populations in these regions. The proportion of sex cord-stromal tumours was
328 less than 2% in most countries, but much higher in some European countries.
329 These differences are also important in the comparison of survival from
330 ovarian cancers combined, because survival is much higher for sex cord-
331 stromal tumours than for epithelial ovarian cancers(23).

332

333 Variation in the distribution of morphological groups of ovarian cancer may

334 impact international comparisons of survival from all ovarian cancers
335 combined if countries with more favourable morphological distributions, where
336 more tumours are classified as type I epithelial, germ cell or sex cord-stromal,
337 are compared to survival in countries with higher proportions of type II
338 epithelial tumours. In the main CONCORD-2 analysis(4), age-standardised 5-
339 year survival from all ovarian tumours combined was higher in some East
340 Asian countries than in Europe, North America and Oceania. In Hong Kong, 5-
341 year survival was 52.9% for women diagnosed from 2005 to 2009, much
342 higher than the highest level of survival in Europe (Finland: 44.9%), North
343 America (US: 40.9%) and Oceania (Australia: 37.5%)(4). The proportion of
344 type I epithelial tumours in Hong Kong (51.7%) was the highest among the 51
345 countries, and Hong Kong was one of only two countries where type I
346 epithelial tumours were more common than type II epithelial tumours. Thus,
347 the higher survival for all ovarian cancers combined in Hong Kong may be
348 partially explained by the more favourable distribution of morphology. A
349 favourable distribution was also seen in Ecuador, with one of the highest
350 proportions of germ cell tumours (7.8%), and age-standardised 5-year survival
351 was 47.0% for all tumours combined(4).

352

353 For many areas of the world, data from population-based cancer registries are
354 still insufficient to allow meaningful comparisons of ovarian cancer
355 morphology. Lack of accurate cancer registration in many areas, and the high
356 proportion of non-specific morphology in many countries, still limits worldwide
357 comparison of survival by morphology.

358

359 During 2005-2009, the highest proportion of tumours of non-specific
360 morphology was seen in Russia (17.7%), which may explain the low
361 proportion of type II epithelial tumours in the country, because many non-
362 specific tumours will be diagnosed at an advanced stage [supplementary
363 Table 4]. In order to classify a tumour as a specific subtype, such as serous or
364 endometrioid, a tissue biopsy or surgical resection is required; thus,
365 morphology may not be correctly classified into a specific subtype if the
366 disease is diagnosed at an advanced stage. In Central and South America,
367 the largest registry (Puerto Rico) provided data only for 684 women, of which
368 24.3% were recorded as having been diagnosed with undifferentiated or other
369 epithelial carcinoma. The accuracy of morphology data is also reliant upon
370 data transmission to the cancer registries and recording of morphology codes,
371 so the distribution of subtypes may be affected by registry procedures and the
372 classifications in use. For example, in Sweden, only 324 of 12,969 (2.5%)
373 women with ovarian cancer were reported as being diagnosed with a specific
374 morphology, compared with 6,311 of 7,322 women (86.2%) in Finland.
375 Previous reports on ovarian cancer in Sweden showed over 98% specific
376 morphology codes(24). Additionally, the distribution for Hong Kong included
377 only epithelial tumours, because other ovarian cancer subtypes were not
378 submitted. While Sweden was excluded from these analyses, Hong Kong was
379 included because comparison of the most common subtypes, type I and type
380 II epithelial, was still achievable.

381

382 Variation between pathologists in the classification of ovarian tumours into
383 specific histological subtypes may affect the distribution of subtypes within a

384 country, and thus, comparisons of the distributions of subtypes between
385 countries. Various studies conducted from 1984 to 1994 of the reproducibility
386 of the World Health Organization's 1973 histological classification of ovarian
387 tumours(25) showed only moderate levels of reproducibility(26). The WHO
388 classification for ovarian tumours was updated in 1999(27), 2003(28) and
389 2014(2). Because tumours diagnosed from 1995 to 2009 were included in the
390 analysis, pathologists could have used either the 1973, 1999 or 2003 criteria
391 to assign a histological subtype to a tumour included in the study. The
392 definitions of the various histological subtypes do not change drastically over
393 time from 1973 to 2003, so the edition used by the pathologist is not
394 necessarily relevant. However, the definitions of the subtypes are general and
395 the 2003 criteria did not include changes or criteria that could improve
396 reproducibility; thus, observer variation remains an issue(26).

397 Studies of immunohistochemical biomarkers and molecular genetic features
398 for certain histological subtypes may allow for more reproducible diagnoses.
399 TP53 mutations are found in 80% of women diagnosed with high-grade
400 serous carcinoma, while KRAS, BRAF and ERBB2 mutations are more
401 common in women with low-grade serous carcinoma. Mutations of CTNNB1,
402 PTEN, PIK3CA are common in endometrioid tumours and KRAS mutations
403 can be found in 50% of mucinous tumours. For clear cell carcinoma,
404 mutations of ARID1A and PIK3CA are common(2, 6, 7, 9). With this
405 knowledge and the updated WHO classification of 2014, reproducibility of the
406 histological typing of ovarian cancers should improve.

407

408 In order to classify serous tumours appropriately into morphological groups,

409 knowledge of the tumour grade is important. However, data on tumour grade
410 are not routinely collected by cancer registries. For ovarian cancer, most
411 serous carcinomas are high-grade, and will have been correctly classified in
412 our analysis as type II epithelial, but a small proportion are low-grade, and
413 should have been classified as type I epithelial(6, 7, 9, 10, 29, 30). Because
414 the proportion of low-grade serous tumours is small(2), the effect of any
415 misclassification on the distribution of morphology is expected to be minimal.
416 The distinction between high-grade and low-grade serous carcinoma is
417 important, because they have a distinct pathogenesis and are thought to be
418 different diseases(6, 7). Low-grade serous carcinoma is more common in
419 younger women, and is thought to arise from borderline serous tumours. In
420 contrast, high-grade serous carcinoma is more common in older women, is
421 thought to arise from tubal disease and typically exhibits p53 mutation(6, 7,
422 31). Similarly, endometrioid tumours are classified as either low- or high-
423 grade, and classification into type I or type II epithelial has previously
424 depended on tumour grade(7). Most endometrioid ovarian tumours will be
425 low-grade(2), and some pathologists have argued that high-grade
426 endometrioid tumours may not exist(7, 10). Distinguishing between high-grade
427 endometrioid and high-grade serous tumours is difficult, and when distinction
428 between endometrioid and serous tumours is unclear, most high-grade
429 tumours may be classified as high-grade serous, because this subtype is
430 more common than high-grade endometrioid(7, 10). Following an update in
431 2016 of the original definitions of type I and type II epithelial tumours, all
432 endometrioid tumours would now be categorised as type I, regardless of
433 tumour grade(6). Future analyses of ovarian cancer survival should, if

434 possible, incorporate a distinction between high- and low-grade serous
435 carcinoma, to reflect the current understanding of ovarian cancer
436 pathogenesis and behaviour, and to classify serous carcinomas appropriately
437 into type I and type II epithelial tumours.

438

439 Carcinoma, NOS (ICD-O-3 morphology code 8010), large cell carcinoma,
440 NOS (8012) and adenocarcinoma, NOS (8140) were categorised as
441 undifferentiated and other epithelial tumours and grouped broadly as type II
442 epithelial. There may also be some misclassification of these tumours,
443 because these morphology codes are not specific codes, so classification into
444 type I or type II is difficult. However, carcinoma (NOS), large cell carcinoma
445 (NOS) and adenocarcinoma (NOS) are treated clinically as if they were high-
446 grade serous carcinomas, which are classified as type II. Therefore, we
447 decided to categorise these tumours as type II epithelial. They comprise
448 20.9% of tumours included in the analysis.

449

450 Only morphologically verified tumours, or those with specific morphologies
451 that implied morphological verification, were included in the analysis. This
452 restriction may affect the distribution of morphological subtypes, because the
453 morphology of advanced-stage tumours that are not fully investigated may be
454 coded as non-specific or unknown. If more advanced-stage tumours are not
455 morphologically verified and therefore excluded from analysis, the distribution
456 of morphological groups may appear more favourable than it actually is.

457

458 This worldwide study of ovarian cancer morphology has identified striking
459 variations in morphological distribution, using data from population-based

460 cancer registries in 51 countries. The two main morphological groups of
461 ovarian cancer have different prognosis, primarily due to differences in the
462 distribution of stage, sensitivity to chemotherapy and response to surgical
463 resection. International comparisons of ovarian cancer survival should take
464 morphology into account, to help identify whether the distribution of
465 morphological type contributes to international differences in ovarian cancer
466 survival, which is typically reported for all morphological subtypes combined.
467 To understand further the impact on survival, we are examining international
468 differences in ovarian cancer survival by morphological group. Registration of
469 both the morphology and the grade of ovarian cancers is important to help
470 categorise these tumours more accurately into morphological groups,
471 especially type I and type II epithelial. Increased support for the development
472 of high-quality population-based cancer registries in low-income countries will
473 also help improve international comparisons of ovarian cancer survival.

474 Word count: 3801

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698 *CONCORD Steering Committee

699

700 **Acknowledgements**

701 We would like to thank Mr. John Butler for proposing the idea for the manuscript.
702 This work was funded by the Canadian Partnership Against Cancer, Cancer Focus
703 Northern Ireland, Cancer Institute New South Wales, Cancer Research UK (C1336/
704 A16148), US Centers for Disease Control and Prevention (CDC; 12FED03123,
705 ACO12036), Swiss Re, Swiss Research foundation, Swiss Cancer League, and the
706 University of Kentucky (3049024672-12-568).

707 **Conflict of interest**

708 The authors declare there are no conflicts of interest.

709 **References**

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786 **List of tables**787 **Table 1.** Ovarian cancer morphological groups and subtypes^a788 ^a No information on grade was available, therefore all endometrioid tumours were
789 classified as type I epithelial.790 ^b No information on grade was available, therefore all serous tumours were classified
791 as type II epithelial792 ^c Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473)
793 were excluded from the analysis of distribution of morphological subtypes (see text).

794

795 **Table 2.** Distribution of morphological groups by continent and calendar period of
796 diagnosis^a797 ^a Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473)
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802 as type II epithelial.803 ^d Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. Only
804 countries with at least 100 women in any given time period were included. All
805 tumours with a specific ICD-O-3 morphology code were included.

806

807 **Supplementary Table 1.** Distribution of ovarian cancer by morphological group and
808 calendar period of diagnosis^a809 ^a Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473)
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818

819 **Supplementary Table 2.** Distribution of type I and type II epithelial subtypes by
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824 classified as type I epithelial.825 ^c No information on grade was available, therefore all serous tumours were classified
826 as type II epithelial.827 ^d Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. Only

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850 as type II epithelial.

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860 classified as type I epithelial.

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862 as type II epithelial.

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