

## Cohort Profile

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## Cohort Profile

# Cohort Profile: The Ovarian Cancer Cohort Consortium (OC3)

Mary K Townsend <sup>1</sup>, Britton Trabert <sup>2</sup>, Renée T Fortner,<sup>3</sup>  
 Alan A Arslan,<sup>4</sup> Julie E Buring,<sup>5,6,7</sup> Brian D Carter,<sup>8</sup> Graham G Giles,<sup>9,10,11</sup>  
 Sarah R Irvin,<sup>12</sup> Michael E Jones,<sup>13</sup> Rudolf Kaaks <sup>3</sup>,  
 Victoria A Kirsh,<sup>14,15</sup> Synnove F Knutsen,<sup>16</sup> Woon-Puay Koh,<sup>17,18</sup>  
 James V Lacey Jr,<sup>19</sup> Hilde Langseth,<sup>20,21</sup> Susanna C Larsson <sup>22</sup>,  
 I-Min Lee,<sup>5,6,7</sup> María Elena Martínez,<sup>23</sup> Melissa A Merritt,<sup>24</sup>  
 Roger L Milne,<sup>9,10,11</sup> Katie M O'Brien,<sup>25</sup> Michael J Orlich <sup>16</sup>,  
 Julie R Palmer,<sup>26</sup> Alpa V Patel,<sup>8</sup> Ulrike Peters,<sup>27,28</sup> Jenny N Poynter,<sup>29</sup>  
 Kim Robien <sup>30</sup>, Thomas E Rohan,<sup>31</sup> Lynn Rosenberg <sup>26</sup>,  
 Sven Sandin,<sup>32,33,34</sup> Dale P Sandler <sup>25</sup>, Leo J Schouten <sup>35</sup>,  
 V Wendy Setiawan <sup>36</sup>, Anthony J Swerdlow <sup>37</sup>,  
 Giske Ursin <sup>38,39,40</sup>, Piet A van den Brandt <sup>35</sup>, Kala Visvanathan,<sup>41,42</sup>  
 Elisabete Weiderpass <sup>43</sup>, Alicja Wolk,<sup>44,45</sup> Jian-Min Yuan <sup>46,47</sup>,  
 Anne Zeleniuch-Jacquotte,<sup>48</sup> Shelley S Tworoger <sup>1†</sup> and  
 Nicolas Wentzensen <sup>12†\*</sup>

<sup>1</sup>Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA, <sup>2</sup>Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA, <sup>3</sup>Division of Cancer Epidemiology, German Cancer Research Centre (DKFZ), Heidelberg, Germany, <sup>4</sup>Division of Epidemiology, Departments of Obstetrics and Gynecology, Population Health, and Environmental Medicine, New York University School of Medicine, New York, NY, USA, <sup>5</sup>Department of Medicine, Harvard Medical School, Boston, MA, USA, <sup>6</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA, <sup>7</sup>Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA, <sup>8</sup>Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, GA, USA, <sup>9</sup>Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, VIC, Australia, <sup>10</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia, <sup>11</sup>Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia, <sup>12</sup>Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA, <sup>13</sup>Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK, <sup>14</sup>Ontario Health Study, Ontario Institute for Cancer Research, Toronto, ON, Canada, <sup>15</sup>Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, <sup>16</sup>School of Public Health, Loma Linda University, Loma Linda, CA, USA, <sup>17</sup>Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, <sup>18</sup>Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A\*STAR), Singapore, Singapore, <sup>19</sup>Beckman Research Institute, City of Hope, Duarte, CA, USA, <sup>20</sup>Department of Research, Cancer Registry of Norway, Oslo, Norway, <sup>21</sup>Department of Epidemiology and Biostatistics, Imperial

College London, London, UK, <sup>22</sup>Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, <sup>23</sup>Moore's Cancer Center, University of California, San Diego, La Jolla, CA, USA, <sup>24</sup>Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA, <sup>25</sup>Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA, <sup>26</sup>Slone Epidemiology Center, Boston University School of Medicine, Boston, MA, USA, <sup>27</sup>Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>28</sup>Department of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA, <sup>29</sup>Division of Pediatric Epidemiology and Clinical Research, University of Minnesota, Minneapolis, MN, USA, <sup>30</sup>Department of Exercise and Nutrition Sciences, Milken Institute School of Public Health, George Washington University, Washington, DC, USA, <sup>31</sup>Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA, <sup>32</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, <sup>33</sup>Department of Psychiatry, Icahn School of Medicine, Mount Sinai, New York, NY, USA, <sup>34</sup>Seaver Autism Center for Research and Treatment, Icahn School of Medicine, Mount Sinai, New York, NY, USA, <sup>35</sup>Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands, <sup>36</sup>Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, <sup>37</sup>Division of Genetics and Epidemiology and Division of Breast Cancer Research, Institute of Cancer Research, London, UK, <sup>38</sup>Cancer Registry of Norway, Oslo, Norway, <sup>39</sup>Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway, <sup>40</sup>Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA, <sup>41</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>42</sup>Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>43</sup>Office of the Director, International Agency for Research on Cancer, World Health Organization, Lyon, France, <sup>44</sup>Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, <sup>45</sup>Department of Surgical Sciences, Uppsala University, Uppsala, Sweden, <sup>46</sup>UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA, <sup>47</sup>Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA and <sup>48</sup>Department of Population Health and Department of Environmental Medicine, New York University School of Medicine, New York, NY, USA

<sup>†</sup>Equally contributing authors.

\*Corresponding author. Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E-448, Bethesda, MD 20892-9774, USA.

E-mail: wentzenn@mail.nih.gov

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### Key Features

- The Ovarian Cancer Cohort Consortium (OC3) was established to facilitate prospective studies of ovarian cancer risk factors, biomarkers, risk prediction and outcomes while accounting for ovarian cancer subtypes.
- The consortium currently includes 1.3 million women, among whom 7314 incident invasive epithelial ovarian cancer cases have been identified, enrolled across 23 prospective studies based in the USA or Canada (16 studies), Europe (five studies), Singapore (one study) and Australia (one study).
- The studies' enrolment periods range from 1976 to currently ongoing and the median age at enrolment ranges from 35 to 62 years. Many of the studies enrolled individuals living in a particular region, and others targeted groups with specific shared characteristics, such as religion, occupation, education or participation in a screening programme or randomised trial.
- Data were collected using mailed or online questionnaires or in-person or telephone interviews and laboratory analysis. Of the 21 studies that collected updated exposure and outcome information from participants after baseline, most collected data every 2–5 years. Data are available on body size, reproductive and contraceptive history, use of medications (e.g. postmenopausal hormone therapy, non-steroidal anti-inflammatory drugs) and selected disease diagnoses.
- Collaboration requests are accepted via a contact form on the OC3 website [theoc3.org].

## Why was the consortium set up?

Ovarian cancer is the most common fatal gynaecological malignancy, but its incidence in the general population is low.<sup>1</sup> Due to the lack of effective prevention or early detection approaches and the late clinical presentation, most ovarian cancers are detected at advanced stages with poor outcomes. Two large ovarian cancer screening trials have not shown a meaningful survival benefit in women screened with the cancer antigen 125 (CA-125) blood test and transvaginal ultrasound.<sup>2,3</sup> Known ovarian cancer risk factors are related to high-penetrance genetic mutations (e.g. in *BRCA1* or *BRCA2*), incessant ovulation, hormone exposures and inflammation. With the exception of *BRCA1/2* status, known risk factors poorly predict individual-level risk of developing ovarian cancer, hindering prevention efforts.<sup>4,5</sup> Epithelial ovarian cancers are highly heterogeneous, with multiple subtypes that can be distinguished by morphology and molecular pathways, risk factor profile, degree of aggressiveness and prognosis.<sup>6,7</sup> The four main histological subtypes (histotypes) of ovarian cancer are serous, endometrioid, clear cell and mucinous tumours; the first two types are further distinguished by level of differentiation (grade). There is increasing evidence that ovarian cancer subtypes have different cells of origin, with a subset of high-grade serous cancers likely originating in the Fallopian tubes and some endometrioid cancers deriving from orthotopic or ectopic endometrial cells, and are clearly characterized by different somatic events (e.g. nearly all high-grade serous tumours have p53 mutations whereas other subtypes do not).<sup>8</sup> Whereas precursors in the ovarian surface epithelium have been elusive, there are now several candidate precursors that have been found in the fallopian tubes, such as serous tubal intraepithelial carcinomas.<sup>8,9</sup> Currently there is insufficient evidence regarding risk factors and risk of progression of these putative precursors. Since tubal intraepithelial carcinomas are typically incidental findings in clinical series of patients undergoing salpingectomy and salpingo-oophorectomy, these presumptive precursors cannot be studied in epidemiological cohorts with cancer endpoints.

Much of the understanding about risk factors, genetics and molecular pathways of ovarian cancer has been derived from case-control studies. Case-control studies can accrue large numbers of cases and have made important contributions to establishing risk factor associations and genetic susceptibility, but risk factors and clinical measures are ascertained at or after the time of diagnosis. Recall bias has been shown to affect some risk factor associations for ovarian cancer.<sup>10</sup> Anthropometric measures obtained at

diagnosis, such as weight, can be substantially affected by disease either due to cancer-related weight loss or due to extensive ascites which may increase weight in a subset of cases. Generally, most risk factors established in case-control studies have also been observed in cohort studies. However, case-control studies are unsuitable for most blood- or urine-based biomarker studies of ovarian cancer incidence, which require samples collected before disease development. Prospective cohort studies can provide questionnaire-based exposure data and prospectively collected biospecimens without differential bias by disease status, but due to the rarity of ovarian cancers in the general population, it is challenging to study risk factors and biomarkers for ovarian cancer prospectively in individual cohorts. With the increasing recognition of the substantial heterogeneity of ovarian cancer and the need to study subtypes, it has become virtually impossible to study risk factors in individual prospective studies.

To address the need for well-powered prospective studies with ovarian cancer endpoints, we developed the Ovarian Cancer Cohort Consortium (OC3), a large population-based resource of prospective ovarian cancer cases from a base sample of over 1.3 million women. The OC3 provides a unique resource to conduct studies of ovarian cancer risk factors, biomarkers, risk prediction and outcomes while accounting for ovarian cancer subtypes. The OC3 protocol was approved by the Institutional Review Board of Brigham and Women's Hospital (Protocol # 2012P000378) and the Advarra Institutional Review Board (Protocol # 00022137).

## Who is in the consortium?

The OC3 was initiated through the National Cancer Institute (NCI) Cohort Consortium, a global partnership of more than 55 cohort studies focused on conducting coordinated parallel and pooled analyses to address cancer-related research questions that would be difficult to address in any single cohort.<sup>11</sup> NCI Cohort Consortium members were initially approached in 2010 to participate in the OC3. Cohorts that prospectively ascertained ovarian cancer diagnoses and collected basic epidemiological data, including oral contraceptive use and parity, were eligible to join. Availability of biospecimens or information on ovarian histotypes was considered a plus but not a prerequisite and there was no minimum number of participants or ovarian cancer cases required. Currently, there are 23 studies in the OC3, including 21 full cohort studies and two case-cohort studies (CSDLH and NLCS; see [Table 1](#)

**Table 1** Descriptive information on OC3 cohorts

Study name	Abbreviation	Institution	Country	Enrolment period	OC3 sample size <sup>a</sup>	Median baseline age, years	Latest year of follow-up in OC3 dataset	Follow-up questionnaires? (active or passive follow-up)
Adventist Health Study II	AHS2	Loma Linda University	USA, Canada	2001–07	39 059	53	2015	Yes (active)
Black Women's Health Study <sup>b</sup>	BWHS	Boston University	USA	1995	59 000	38	NA	Yes (active)
Breast Cancer Detection Demonstration Project	BCDDP	National Cancer Institute	USA	180	36 395	61	1999	Yes (passive)
California Teachers Study	CTS	City of Hope	USA	1995–96	44 176	50	2012	Yes (active)
Campaign Against Cancer and Stroke	CLUEII	Johns Hopkins	USA	1989	12 395	46	2012	Yes (passive)
Canadian Study of Diet, Lifestyle, and Health <sup>c</sup>	CSDLH	Canadian Study of Diet, Lifestyle, and Health	Canada	1992–98	3019 (39 618)	58	2011	Yes (passive)
Cancer Prevention Study-II	CPSII	American Cancer Society	USA (incl. Puerto Rico)	1982	82 435	62	2009	Yes (passive)
Cancer Prevention Study-3 <sup>b</sup>	CPS3	American Cancer Society	USA (incl. Puerto Rico)	2006–13	198 580	47	NA	Yes (active)
European Prospective Investigation into Cancer and Nutrition	EPIC	International Agency for Research on Cancer/German Cancer Research Center	France, Italy, Spain, UK, The Netherlands, Germany, Sweden, Denmark, Norway	1992–2000	249 489	51	2010	Yes (active)
Generations Study (formerly Breakthrough Generations Study)	BGS	Institute of Cancer Research	UK	2003–13	101 894	48	2014	Yes (active)
Iowa Women's Health Study	IWHS	University of Minnesota/ University of Iowa	USA	1986	30 671	61	2011	Yes (passive)
Janus Serum Bank <sup>b</sup>	JSB	Cancer Registry of Norway	Norway	1972–2004	152 491	42	NA	No (passive)
Melbourne Collaborative Cohort Study	MCCS	Cancer Council Victoria	Australia	1990–94	20 863	55	2010	Yes (passive)
Multiethnic Cohort Study (White women only)	MEC	University of Hawaii/ University of Southern California	USA	1993–96	16 510	57	2012	Yes (active)
Netherlands Cohort Study <sup>c</sup>	NLCS	Maastricht University	The Netherlands	1986	2883 (62 573)	62	2010	No (passive)
NIH-AARP Diet and Health Study	AARP	National Cancer Institute at the National Institutes of Health	USA	1995–96	201 510	62	2007	Yes (passive)
Nurses' Health Study	NHS	Brigham and Women's Hospital	USA	1976	98 605	47	2010	Yes (active)
Nurses' Health Study II	NHSII	Harvard T.H. Chan School of Public Health	USA	1989	114 033	35	2011	Yes (active)
NYU Women's Health Study	NYUWHS	New York University	USA	1985–91	12 439	49	2012	Yes (active)
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	PLCO	National Cancer Institute	USA	1993–2001	60 846	62	2009	Yes (passive)

(Continued)

Table 1 Continued

Study name	Abbreviation	Institution	Country	Enrolment period	OC3 sample size <sup>a</sup>	Median baseline age, years	Latest year of follow-up in OC3 dataset	Follow-up questionnaires? (active or passive follow-up)
Singapore Chinese Health Study	SCHS	National University of Singapore	Singapore (Chinese participants)	1993–98	34 021	56	2012	Yes (active)
Sister Study	SIS	National Institute of Environmental Health Sciences	USA (incl. Puerto Rico)	2003–09	48 163	56	2012	Yes (active)
Swedish Mammography Cohort	SMC	Uppsala University/Karolinska Institutet	Sweden	1987–90	37 205	60	2012	Yes (passive)
Vitamins and Lifestyle Study	VITAL	Fred Hutchinson Cancer Research Center	USA	2000–02	28 343	60	2011	No (passive)
Women's Health Study	WHS	Brigham and Women's Hospital	USA	1992–95	39 807	53	2012	Yes (active)
Swedish Women's Lifestyle and Health	WLH	Karolinska University	Sweden	1991–92	49 229	40	2013	Yes (passive)

NA, not applicable; OC3, Ovarian Cancer Cohort Consortium.

<sup>a</sup>The OC3 study population is restricted to women with a non-missing age at baseline questionnaire return, a non-missing age at censoring event (i.e. ovarian cancer diagnosis, death or latest follow-up, whichever is earliest), a censoring event that occurred after baseline and no history of cancer before baseline. For the case-cohort studies, the total number of women in the full cohort is shown in parentheses.

<sup>b</sup>Study is currently in the process of joining OC3; sample size and median age at baseline are based on female participants in the whole cohort.

<sup>c</sup>Case-cohort study design.

for full study names), and three additional cohorts (BWHS, CPS3, JSB) are in the process of joining.

Of the 26 studies, 18 are based in the USA or Canada, six in Europe, one in Asia and one in Australia (Table 1). The studies' enrolment periods range from 1972 to currently ongoing. Many of the studies sought to enrol individuals in the general population of a particular region and used a variety of registries to identify potential participants [e.g. driver's licence list (IWHS, MEC), electoral roll and phone directory (MCCS), population registry (NLCS, WLH) or commercial mailing list (VITAL)]. However, several studies targeted groups with specific shared characteristics, such as religion (AHS2), occupation or education (CTS, NHS, NHSII, CSDLH), enhanced breast cancer risk (SIS) or screening programme participation (BCDDP, NYUWHS, SMC). Two studies are observational extensions of randomized trials (PLCO, WHS).

When considering only participants that are typically eligible for OC3 analyses (see Supplementary Methods, available as Supplementary data at IJE online) and excluding three studies that have not yet submitted data to the OC3 (BWHS, CPS3 and JSB), the median study size is 39 059 women (interquartile range = 20 863 to 82 435) and the total pooled population in the consortium is 1 363 990 women. After the addition of BWHS, CPS3 and JSB, the total pooled population will be approximately 1.7 million women. The median age at enrolment was 50 years or older for 17 of the 23 studies (Table 1).

The current pooled OC3 dataset (median end of follow-up = 2011; Table 1) includes 7314 incident invasive epithelial ovarian cancer cases, of whom 5109 (69.9%) have data on histotype (Table 2). Of the 7314 cases, 50% are from four studies (AARP, NHS, EPIC, CPS2) with each contributing 8–18% of the total number of cases. The addition of BWHS, CPS3 and JSB is expected to add more than 2000 invasive ovarian cancer cases to the OC3.

In all the OC3 studies except SCHS, serous cancer was the histotype in the majority of cases, followed by endometrioid and mucinous cancers, which have similar prevalence, and clear cell cancer, the least common of the four major histotypes (Supplementary Figure S1, available as Supplementary data at IJE online). This distribution is consistent with observations in previous studies focused on women of European ancestry.<sup>12,13</sup> SCHS, which enrolled Chinese adults living in Singapore, is unique in that the serous histotype is observed in less than half of the cases, and mucinous and clear cell tumours are more common than in the other studies. This distribution is consistent with international registry data showing a greater prevalence of clear cell tumours among Asian versus White women.<sup>14</sup> Pooled case numbers are 3794 for serous, 664 for endometrioid, 356 for mucinous and 295 for clear cell. Moreover, case

**Table 2** Distribution of the four major ovarian cancer histotypes by study in OC3<sup>a</sup>

Study abbreviation	All invasive epithelial ovarian cancer cases		All invasive epithelial ovarian cancer cases classified as one of the four major histotypes		Serous or poorly differentiated		Endometrioid		Mucinous		Clear cell	
	Median age at diagnosis	<i>n</i> (%)	Median age at diagnosis	<i>n</i> (%)	Median age at diagnosis	<i>n</i> (%) <sup>b</sup>	Median age at diagnosis	<i>n</i> (%) <sup>b</sup>	Median age at diagnosis	<i>n</i> (%) <sup>b</sup>	Median age at diagnosis	<i>n</i> (%) <sup>b</sup>
<b>USA and Canada</b>												
AARP	69.9	1350 (18.5)	68.0	701 (13.7)	68.4	546 (77.9)	65.3	85 (12.1)	66.8	44 (6.3)	64.8	26 (3.7)
AHS2	67.7	98 (1.3)	65.4	67 (1.3)	66.4	45 (67.2)	61.6	13 (19.4)	79.8	5 (7.5)	65.2	4 (6.0)
BCDDP	68.5	175 (2.4)	68.0	96 (1.9)	69.0	67 (69.8)	66.0	21 (21.9)	74.0	5 (5.2)	58.0	3 (3.1)
CSDLH	62.7	112 (1.5)	60.0	72 (1.4)	65.5	40 (55.6)	53.6	14 (19.4)	57.4	10 (13.9)	46.0	8 (11.1)
CLUEII	66.5	90 (1.2)	64.0	52 (1.0)	64.0	39 (75.0)	62.0	9 (17.3)	54.0	2 (3.8)	69.5	2 (3.8)
CPS2	70.0	578 (7.9)	70.0	455 (8.9)	70.0	358 (78.7)	69.0	51 (11.2)	68.0	26 (5.7)	69.0	20 (4.4)
CTS	66.0	216 (3)	65.0	161 (3.2)	68.0	104 (64.6)	61.0	29 (18.0)	70.0	7 (4.3)	56.0	21 (13.0)
IWHS	74.0	380 (5.2)	73.0	242 (4.7)	73.0	194 (80.2)	71.5	20 (8.3)	69.0	17 (7.0)	73.0	11 (4.5)
MEC	69.4	104 (1.4)	67.6	64 (1.3)	68.7	49 (76.6)	65.8	6 (9.4)	71.0	4 (6.3)	56.5	5 (7.8)
NHS	65.9	910 (12.4)	65.8	818 (16.0)	66.6	626 (76.5)	62.7	110 (13.4)	62.0	42 (5.1)	62.1	40 (4.9)
NHS2	51.2	282 (3.9)	50.8	230 (4.5)	51.3	136 (59.1)	49.6	49 (21.3)	45.7	12 (5.2)	52.3	33 (14.3)
NYUWHS	63.9	136 (1.9)	63.9	104 (2.0)	64.8	81 (77.9)	57.1	7 (6.7)	64.5	8 (7.7)	57.8	8 (7.7)
PLCO	70.0	412 (5.6)	70.0	273 (5.3)	70.0	230 (84.2)	65.0	23 (8.4)	64.0	8 (2.9)	70.0	12 (4.4)
SIS	58.6	47 (0.6)	58.0	36 (0.7)	58.0	28 (77.8)	59.7	4 (11.1)	NA	NA	56.3	4 (11.1)
VITAL	67.6	142 (1.9)	67.1	106 (2.1)	68.0	89 (84.0)	62.6	8 (7.5)	71.9	3 (2.8)	62.9	6 (5.7)
WHS	63.4	207 (2.8)	63.3	158 (3.1)	63.6	131 (82.9)	60.4	20 (12.7)	65.0	7 (4.4)	NA	NA
<b>Europe</b>												
BGS	62.1	104 (1.4)	62.1	70 (1.4)	62.6	48 (68.6)	53.2	5 (7.1)	67.6	13 (18.6)	54.7	4 (5.7)
EPIC	62.6	837 (11.4)	61.9	602 (11.8)	62.9	435 (72.3)	59.6	81 (13.5)	59.5	49 (8.1)	59.9	37 (6.1)
NLCS	71.0	471 (6.4)	70.0	333 (6.5)	71.0	240 (72.1)	70.0	37 (11.1)	68.0	41 (12.3)	68.0	15 (4.5)
SMC	67.7	213 (2.9)	67.0	161 (3.2)	66.9	116 (72.0)	67.4	30 (18.6)	76.3	10 (6.2)	63.4	5 (3.1)
WLHS	53.8	224 (3.1)	54.2	129 (2.5)	54.3	89 (69.0)	52.8	18 (14.0)	53.3	15 (11.6)	54.3	7 (5.4)
<b>Other regions</b>												
MCCS	68.7	107 (1.5)	68.7	88 (1.7)	69.5	61 (69.3)	63.6	9 (10.2)	61.5	10 (11.4)	65.0	8 (9.1)
SCHS	63.2	119 (1.6)	61.2	91 (1.8)	64.3	42 (46.2)	60.9	15 (16.5)	59.3	18 (19.8)	60.8	16 (17.6)
<b>All studies</b>	<b>66.5</b>	<b>7314 (100)</b>	<b>65.4</b>	<b>5109 (100)</b>	<b>67.0</b>	<b>3794 (74.2)</b>	<b>62.9</b>	<b>664 (13.0)</b>	<b>64.1</b>	<b>356 (7.0)</b>	<b>61.2</b>	<b>295 (5.8)</b>

NA, not applicable; OC3, Ovarian Cancer Cohort Consortium.

<sup>a</sup>See Table 1 for full study names corresponding to each abbreviation. BWHS, CPS3 and JSB are not included in this table because they have not yet contributed data to the OC3.

<sup>b</sup>Percentages represent the proportion of cases of each histotype, among cases classified as one of the four major histotypes within each study.

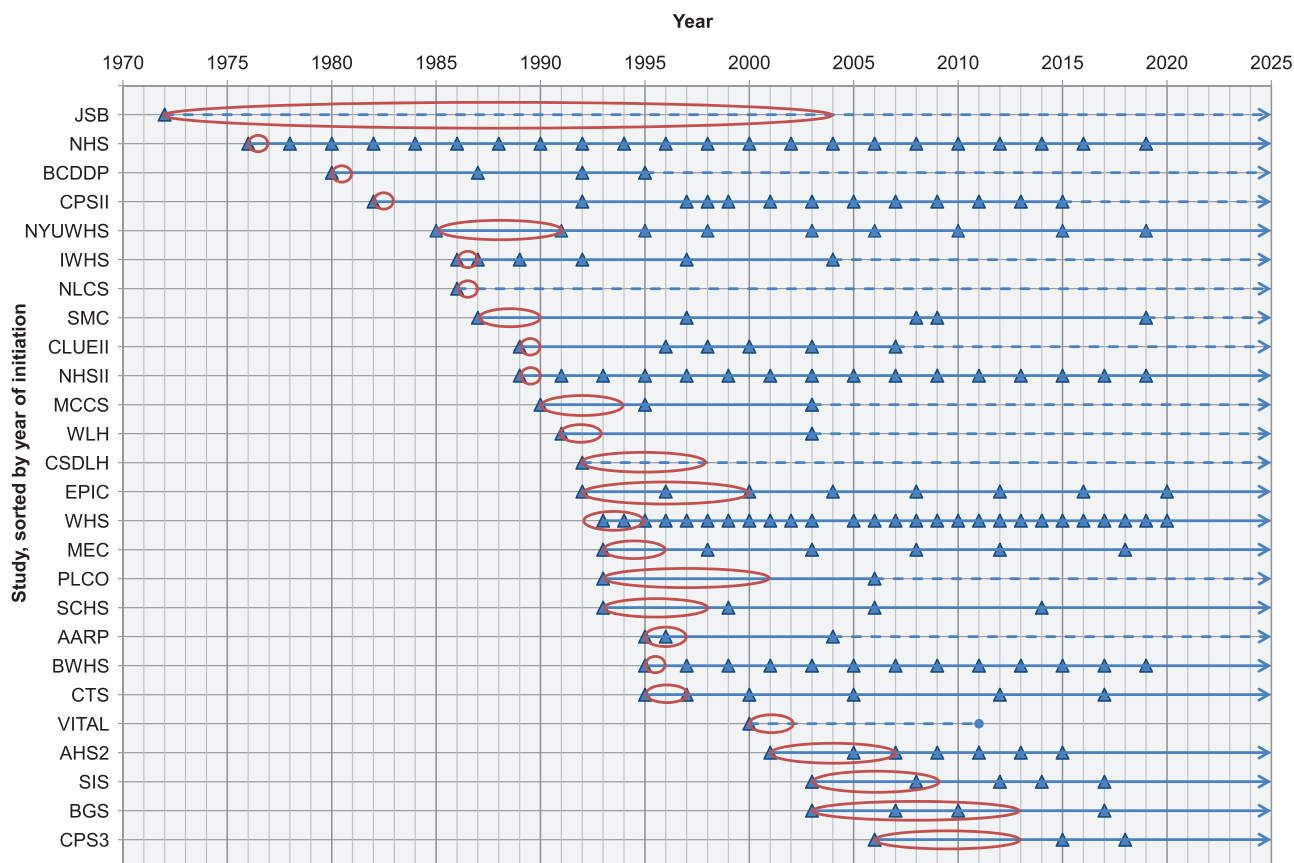
numbers for serous and endometrioid tumours by grade are large enough to allow for exploration of potential differences in risk factor associations by grade (Supplementary Table S1, available as Supplementary data at *IJE* online).

### How often have they been followed up?

Mailed or online questionnaires were the primary mode of data collection across all the studies, although a few studies incorporated face-to-face or telephone interviews with participants to collect data. Of the 23 studies, 21 sent at least one follow-up questionnaire to participants (or conducted follow-up interviews) to collect updated exposure and outcome information after baseline (Table 1, Figure 1). The interval between questionnaires ranged from annually to 13 years, with most studies collecting data every 2–5 years. Currently, 11 studies are actively following participants through periodic questionnaires or in-person interviews. However, most studies that are no longer actively contacting participants continue to passively follow them for cancer diagnosis and death via linkage with cancer and death registries.

### What has been measured?

To initiate the consortium, the OC3 data coordinating centre requested baseline questionnaire data from each study as well as information on ovarian cancer diagnoses and deaths that had been ascertained in the study (see Supplementary Methods for details about procedures for requesting data and harmonizing variables). Information on body mass index, menarche and menopause, parity, oral contraceptive use, hysterectomy and oophorectomy status, postmenopausal hormone therapy use, and several other putative risk factors (e.g. alcohol intake, smoking, diabetes, cardiovascular disease, aspirin use) are consistently available across many of the studies (Table 3). The studies identify cancer cases and case characteristics (e.g. stage, histotype, morphology, grade) either through participant self-reports on questionnaires with subsequent confirmation by review of pathology reports or through linkage with regional or national cancer registries, or a combination of the two methods. Histotype was coded by the individual studies using International Classification of Diseases for Oncology codes,<sup>15</sup> and the data coordinating centre created a consensus codebook to classify histotype in



**Figure 1** Timing of questionnaires in the Ovarian Cancer Cohort Consortium, by study.

See Table 1 for full study names corresponding to each abbreviation. Triangles indicate a questionnaire mailing or interview. Ovals indicate the study enrolment period. Solid arrow lines indicate studies that are still actively following participants (i.e., planning to send additional questionnaires or conduct additional interviews to collect updated exposure and/or disease information). Dotted arrow lines indicate studies that no longer actively follow participants but are passively collecting participant endpoints via linkage with cancer and death registries. The countries within the European Prospective Investigation into Cancer and Nutrition (EPIC) collect data at different time intervals; data are shown for the country within EPIC with the shortest interval between questionnaires.



**Table 3** Availability of data on known and suspected ovarian cancer risk factors at baseline, cause of death and ovarian cancer treatment, and biospecimens collected in each OC3 study<sup>a</sup>

Variable	AARP	AHS2	BCDDP	BGS	CLUEII	CPS2	CSDLH	CTS	EPIC	IWHS	MCCS	MEC	NHS	NHSII	NLCS	NYUWHS	PLCO	SCHS	SMC	SIS	VITAL	WHS	WLH
<b>Anthropometric variables</b>																							
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body mass index in young adulthood <sup>b</sup>	X	X		X	X	X	X	X		X		X	X	X	X				X		X		X
Body mass index at baseline	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Menarche and menopause variables</b>																							
Age at menarche	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Menopausal status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Age at natural menopause	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reason for menopause	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Reproductive history</b>																							
Parity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Age at first birth	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Age at latest birth				X				X	X	X	X		X	X						X			X
Duration of breastfeeding		X		X			X	X	X		X		X	X						X			X
<b>Contraception history</b>																							
Tubal ligation		X				X		X	X				X	X	X	X	X		X	X	X	X	
Ever used oral contraceptives	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral contraceptive use duration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Age first used oral contraceptives			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Age last used oral contraceptives				X		X	X	X	X		X			X	X	X				X			
<b>Family history of breast or ovarian cancer</b>																							
1st degree family history of breast cancer	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
1st degree family history of ovarian cancer	X	X	X	X	X	X		X		X		X	X	X	X		X	X		X	X	X	
<b>Hysterectomy/oophorectomy status</b>																							
Hysterectomy status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oophorectomy status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Postmenopausal use of hormone therapy</b>																							
Postmenopausal HT use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Duration of postmenopausal HT use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ever use of oral oestrogen only	X	X		X		X	X	X				X	X					X		X	X	X	
Duration of use of oral oestrogen only	X	X		X		X	X					X	X					X		X	X	X	
Ever use of oral oestrogen+progestin only	X	X	X	X		X	X	X				X	X					X	X	X	X	X	
Duration of use of oral oestrogen+progestin	X	X	X	X		X	X					X	X					X	X	X	X	X	
Ever use of other postmenopausal HT		X		X		X	X	X					X							X			
		X		X		X	X						X							X			

(Continued)

**Table 3 Continued**

Variable	AARP	AHS2	BCDDP	BGS	CLUEII	CPS2	CSDLH	CTS	EPIC	IWHS	MCCS	MEC	NHS	NHSII	NLCS	NYUWHS	PLCO	SCHS	SMC	SIS	VITAL	WHS	WLH	
Duration of use of other postmenopausal HT																								
<b>Other putative risk factors</b>																								
Endometriosis					X			X		X				X			X		X	X		X	X	
Alcohol intake	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pack-years (among ever smokers)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiovascular disease	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diabetes	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ever diagnosed with autoimmune disease								X					X						X	X	X	X	X	X
Ever diagnosed with PID								X											X	X		X	X	X
Regular aspirin or NSAID use	X			X	X	X	X					X	X	X	X	X	X		X	X	X	X	X	X
Race	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Education	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Diet <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Cause of death, ovarian cancer treatment</b>																								
Treatment data from pathology, surgical reports, or tumour registry				X				X		X		X				X				X	X	X	X	X
Cause of death		X		X		X		X	X	X	X	X	X	X	X	X		X	X		X	X	X	X
<b>Biospecimens<sup>d</sup></b>																								
Blood		(X)		X	X	X		X	X		X	(X)	(X)	(X)		X	X	X	(X)	X		X		X
Urine		(X)		(X)							X	(X)	(X)	(X)				X	(X)	X				
Buccal cells						X							(X)	(X)				X	(X)	(X)	X			
Ovarian tumour tissue				X						X	X		X	X	X		X			X		X		X

HT, hormone therapy; NSAID, non-steroidal anti-inflammatory drug; OC3, Ovarian Cancer Cohort Consortium; PID, pelvic inflammatory disease.

<sup>a</sup>See Table 1 for full study names corresponding to each abbreviation. BWHS, CPS3, and JSB are not included in this because they have not yet contributed data to the OC3.

<sup>b</sup>For BMI in young adulthood, all studies used recalled weight at age 18 except AHS2, CSDLH and PLCO which used age 20, and CLUEII which used age 21.

<sup>c</sup>Data on diet were collected after baseline in some studies.

<sup>d</sup>(X) indicates that a subset of the study population was targeted for biospecimen collection; X (without parentheses) indicates that the study attempted to collect the biospecimen in the whole study population.

alignment with the World Health Organization classification (first revision).<sup>16</sup> Almost all the studies confirm deaths through linkage with regional or national death registries. Details about ovarian cancer treatment and cause of death are available in a subset of studies (Table 3).

Prospectively collected biospecimens are available in many of the studies (Table 3). Blood was the most commonly collected biospecimen in the studies. Given the prospective blood collection, there is a unique opportunity in the OC3 to examine whether a biomarker-risk association varies by timing of blood collection in relation to ovarian cancer diagnosis. Blood was collected 5 or more years before ovarian cancer diagnosis for 60% of ovarian cancer cases, providing an opportunity to study a range of biomarkers related to aetiology and natural history (Supplementary Table S2, available as Supplementary data at *IJE* online). Blood was collected within 3 years before diagnosis for 23% of cases, highlighting the potential to conduct studies of biomarkers for early detection. Germline DNA is also available in many studies for all or some participants and several have collected buccal cells and urine. The subset of participants who provided blood or buccal cell samples tended to be younger and more likely to have ever used oral contraceptives, be premenopausal and have shorter duration of postmenopausal hormone therapy use than all participants in the OC3 (Supplementary Table S3, available as Supplementary data at *IJE* online). This is largely explained by the influence of NHSII, which has the youngest participants of all the OC3 studies (median age at enrolment = 35 years) and collected biospecimens from more than 29 600 women.

Measurement of tissue markers by immunohistochemistry, or newer approaches such as multiplex immunofluorescence, holds promise for a deeper understanding of the mechanisms underlying associations between risk factors and cancer risk. In this regard, some of the OC3 studies have received, or continue to request, consent from participants diagnosed with ovarian cancer to obtain ovarian tumour tissue from the hospitals where participants were treated, or have tissue blocks or tissue microarrays available for research purposes (Table 3).

The consortium has received funding to request additional variables from the member studies, including data from follow-up questionnaires and updated information on cancer incidence and deaths. The consortium will continue to expand the pooled dataset as more projects are funded.

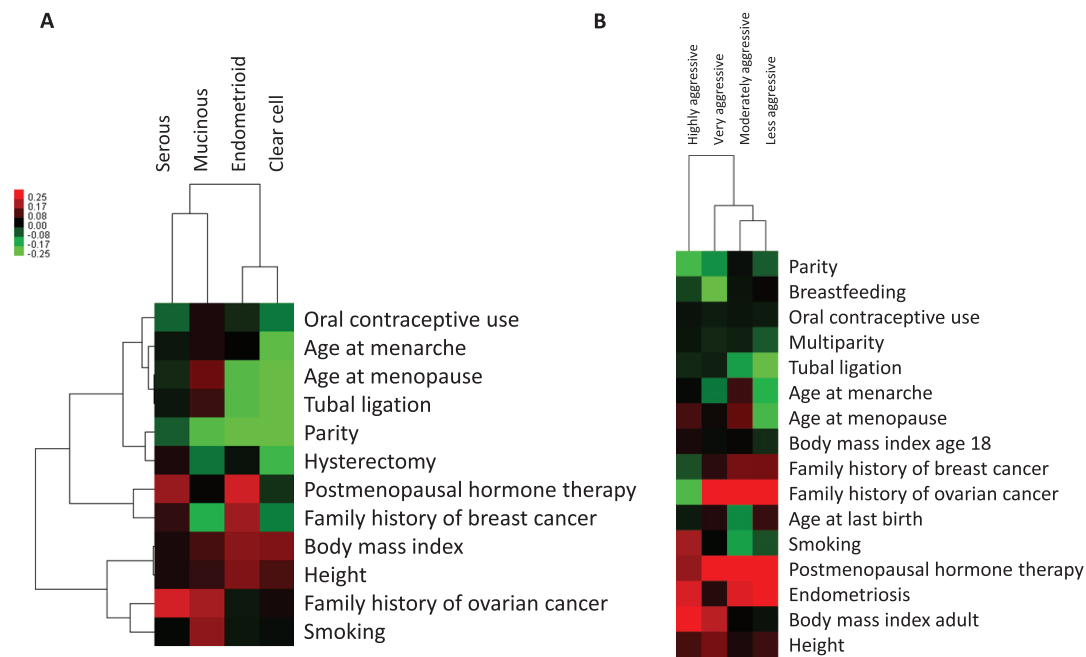
### What has been found?

Several pooled analyses of risk factor data and of previously measured biomarker data have been published by the

OC3 (see Supplementary Methods for the general approach to statistical analyses in the OC3). Depending on the availability of exposure and biomarker data, the analyses included different subsets of OC3 cohorts.

Ovarian cancers can be subdivided by various characteristics, including histotype, tumour aggressiveness (based on survival time) and anatomical location of presentation (ovary, fallopian tube, peritoneum). The first paper from the OC3 found substantial heterogeneity of 12 risk factor associations by histotype, with the weakest associations observed for most risk factors with serous tumours, the most common and aggressive subtype of ovarian cancer.<sup>7</sup> Unsupervised clustering of selected risk factors highlighted similar risk factor patterns between endometrioid and clear cell tumours (Figure 2A). When evaluating risk factors by tumour aggressiveness, several risk factors, particularly high body mass index (BMI) and cigarette smoking, were associated with more aggressive, rapidly fatal ovarian cancer, which could reflect a combination of factors such as tumour biology, access to care and/or treatment response (Figure 2B).<sup>17</sup> The heterogeneity was not fully explained by histotype, suggesting that both histotype and tumour aggressiveness contribute independently to ovarian cancer heterogeneity. A separate analysis found that most risk factor associations did not vary by anatomical site, except for age at first pregnancy, tubal ligation and early-adult BMI.<sup>18</sup> Currently, there is not a single classification that by itself distinguishes aetiological or clinically meaningful subgroups of ovarian cancers. In the future, molecular classifications based on immunohistochemistry and molecular profiling will be used to further classify ovarian cancers and study risk factor and biomarker associations.<sup>19–21</sup>

Several OC3 studies have focused on inflammation-related exposures or biomarkers. Of these, two examined sources of inflammation that might influence cancer risk via direct impact on the ovaries or fallopian tubes [lifetime ovulatory cycles (LOCs)<sup>22</sup> and genital powder use<sup>23</sup>]. The LOC analysis precisely quantified the risk associated with number of ovulatory cycles and showed heterogeneity by ovarian cancer subtype. Further, LOCs were independently associated with ovarian cancer risk after adjusting for the individual contributors to LOC calculations. Regarding genital powder use, previous findings were primarily based on case-control studies that are at risk of recall bias, and the few prospective studies were underpowered to find weaker risk associations. In the largest prospective study so far, the OC3 found a very small, positive association between genital powder use and ovarian cancer risk among all women [hazard ratio (HR) 1.08, 95% confidence interval (CI) 0.99–1.17] as well as among women with intact uterus and fallopian tubes (HR 1.13, 95% CI 1.01–1.26).<sup>23</sup> Other potential risk factors examined in the OC3



**Figure 2** Unsupervised hierarchical clustering of ovarian cancer subtypes by their associations with risk factors.

Unsupervised hierarchical clustering of (A) the four major ovarian cancer histotypes and (B) four ovarian tumour aggressiveness categories (highly aggressive = time between diagnosis and death <1 year; very aggressive = death in 1 to <3 years; moderately aggressive = death in 3 to <5 years; less aggressive = lived  $\geq$ 5 years). Unless otherwise noted, the categories used in the cluster analysis were ever versus never parous, ever versus never oral contraceptive use, ever versus never tubal ligation, ever versus never endometriosis, age at menarche >15 vs  $\leq$ 11 years, age at menopause <40 versus 50 to 55 years, ever versus never menopausal hormone therapy use, ever versus never hysterectomy, family history of breast cancer (yes vs no), family history of ovarian cancer (yes vs no), body mass index >35 versus 20 to 25 kg/m<sup>2</sup>, height (per 5-cm increase), and ever versus never smoking. The colour scale shows the range of  $\beta$ -values for each exposure.

reflect systemic exposure to inflammation. For example, in a pooled evaluation in a subset of OC3 cohorts with previously measured plasma or serum C-reactive protein (CRP), CRP concentrations >10 versus <1 mg/L were associated with more than 3-fold increased risks of endometrioid and mucinous cancers.<sup>24</sup> A study of analgesic use and ovarian cancer risk from the OC3 confirmed findings from previous case-control studies showing an inverse association between frequent use of aspirin, a non-steroidal anti-inflammatory drug, and risk of ovarian cancer. No subtype heterogeneity in this association was observed.<sup>25</sup> A complete list of OC3 publications can be found at [theoc3.org/research].

### What are the main strengths and weaknesses?

Major strengths of the consortium are the large prospective dataset of more than 1.3 million women, including more than 7300 incident ovarian cancer cases, and extensive data on histotype which permit conduct of well-powered studies of risk factors and biomarkers in ovarian cancer subtypes. The consortium setting enables relatively quick evaluation of the reproducibility of associations across

many study populations. The cohort studies have a rich set of risk factor data covering all established ovarian cancer risk factors and many other exposures that could be relevant for specific ovarian cancer subtypes. A subset of OC3 studies has prospective blood collections, and a few have repeated blood samples, allowing conduct of well-powered biomarker studies including research to identify or validate markers of early detection. Furthermore, several studies in the OC3 have tissue specimens available that enable molecular studies designed to understand ovarian cancer aetiology and to evaluate molecular subtypes. The OC3 is closely connected to the Ovarian Cancer Association Consortium (OCAC), the largest consortium of ovarian cancer studies, which includes primarily case-control studies and clinical case series focused on genetic association studies but has also a strong epidemiological component. Several projects are under way which will pool data from both consortia, which are particularly suited to study rare exposures in rare subtypes. Furthermore, the OCAC has completed several genome-wide association studies (GWAS) and some cohorts in OC3 contributed case-control sets for genotyping in OCAC. These data and other GWAS sources in OC3 studies create opportunities for studies of risk factor by gene interactions. The OC3 is

ideally situated to validate associations of individual risk factors, genetic susceptibility and integrated risk models developed in OCAC.

However, some weaknesses of the OC3 need to be noted. Although the OC3 includes cohorts from around the world, the racial/ethnic diversity is very limited with only one cohort from Asia and none from Africa, which reflects the few cohort studies conducted in these regions. Most cohorts in the OC3 cover a limited age range at enrolment, which limits the exposure windows that can be studied with biomarkers. Despite the size of the consortium, there is still limited sample size for analyses of rare histotypes. The OC3 database currently only includes exposures measured at baseline, but an ongoing effort is under way to obtain follow-up data in a subset of studies which will enable analyses accounting for time-varying exposures. Biospecimens are only available in a subset of studies, and repeated blood collections are available only in very few studies. The simultaneous evaluation of different exposures and biomarkers may be limited by missing variables and missing data across the studies, but this might be addressed by large-scale imputation approaches.

### How can I access the data?

Making OC3 data widely available for epidemiological studies on ovarian cancer is one of the core missions of the OC3. The OC3 welcomes collaboration requests from studies wishing to join the consortium as well as from researchers seeking to use the data for specific research projects. Researchers do not need to be affiliated with an OC3 member study to submit a study proposal. Research proposals from junior scientists are encouraged. Interested researchers should visit the OC3 website [theoc3.org] to fill out a contact form, view an up-to-date list of currently approved projects and read instructions for proposing a new project. Briefly, to propose a project, the researcher must submit an analysis proposal form which is then circulated to the OC3 Steering Committee for review. OC3 studies have agreed to an opt-in approach for analyses. Therefore, the researcher must obtain approval from the main contact of each study for that study's data to be included in the analysis. Finally, to access data, a data use agreement is set up between the researcher's institution and the data coordinating centre (based at Moffitt Cancer Center) and appropriate institutional review board approvals may need to be obtained. Researchers involved in active analyses participate in bi-weekly analysis calls to provide updates on progress, present preliminary results and receive early feedback. The OC3 website [theoc3.org]

contains further details related to OC3 leadership and policies. Enquiries can also be submitted directly to Dr Shelley Tworoger [shelley.tworoger@moffitt.org]. The data underlying this article were provided by each of the member OC3 studies under a Data Use Agreement with Moffitt Cancer Center. Data will be shared following OC3 analysis proposal guidelines which can be found at [theoc3.org/policies]. These guidelines include approval of an analysis proposal by the OC3 Steering Committee, written approval from the main contact of each study, set-up of a data use agreement between the requestor's institution and Moffitt Cancer Center, and approval by the appropriate institutional review board.

### Supplementary Data

Supplementary data are available at *IJE* online.

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## Author contributions

Author contributions are available as a Supplementary file at IJE online.

## Conflict of interest

None declared.

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