Ovarian Cancer Risk Factor Associations by Primary Anatomic Site

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

Ovarian Cancer Risk Factor Associations by Primary Anatomic Site: The Ovarian Cancer Cohort Consortium

Renée T. Fortner[1], Megan S. Rice[2], Synnove F. Knutsen[3], Michael J. Orlich[3], Kala Visvanathan[4], Alpa V. Patel[5], Mia M. Gaudet[5], Anne Tjønneland[6,7], Marina Kvaskoff[8,9], Rudolf Kaaks[1], Antonia Trichopolou[10], Valeria Pala[11], N. Charlotte Onland-Moret[12], Inger T. Gram[13], Pilar Amiano[14,15], Annika Idahl[16], Naomi E. Allen[17], Elisabete Weiderpass[18], Jenny N. Poynter[19], Kim Robien[20], Graham G. Giles[21,22,23], Roger L. Milne[21,22,23], Veronica W. Setiawan[24], Melissa A. Merritt[25], Piet A. van den Brandt[26], Anne Zeleniuch-Jacquotte[27], Alan A. Arslan[27], Katie M. O'Brien[28], Dale P. Sandler[28], Alicja Wolk[29,30], Niclas Håkansson[29], Holly R. Harris[31,32], Britton Trabert[33], Nicolas Wentzensen[33], Shelley S. Tworoger[34,35], and Leo J. Schouten[26]

ABSTRACT

Background: Epithelial ovarian, fallopian tube, and primary peritoneal cancers have shared developmental pathways. Few studies have prospectively examined heterogeneity in risk factor associations across these three anatomic sites.

Methods: We identified 3,738 ovarian, 337 peritoneal, and 176 fallopian tube incident cancer cases in 891,731 women from 15 prospective cohorts in the Ovarian Cancer Cohort Consortium. Associations between 18 putative risk factors and risk of ovarian, peritoneal, and fallopian tube cancer, overall and for serous and high-grade serous tumors, were evaluated using competing risks Cox proportional hazards regression. Heterogeneity was assessed by likelihood ratio tests.

Results: Most associations did not vary by tumor site ($P_{het} \geq 0.05$). Associations between first pregnancy ($P_{het} = 0.04$), tubal ligation ($P_{het} = 0.01$), and early-adult (age 18–21 years) body mass index (BMI; $P_{het} = 0.02$) and risk differed between ovarian and peritoneal cancers. The association between early-adult BMI and risk further differed between peritoneal and fallopian tube cancer ($P_{het} = 0.03$). First pregnancy and tubal ligation were inversely associated with ovarian, but not peritoneal, cancer. Higher early-adult BMI was associated with higher risk of peritoneal, but not ovarian or fallopian tube, cancer. Patterns were generally similar when restricted to serous and high-grade serous cases.

Conclusions: Ovarian, fallopian tube, and primary peritoneal cancers appear to have both shared and distinct etiologic pathways, although most risk factors appear to have similar associations by anatomic site.

Impact: Further studies on the mechanisms underlying the differences in risk profiles may provide insights regarding the developmental origins of tumors arising in the peritoneal cavity and inform prevention efforts.

[1]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [2]Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts. [3]School of Public Health, Loma Linda University, Loma Linda, California. [4]Johns Hopkins Bloomberg School of Public Health and School of Medicine, Baltimore, Maryland. [5]Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, Georgia. [6]Department of Public Health, University of Copenhagen, Copenhagen, Denmark. [7]Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark. [8]CESP, Fac. de médecine-Univ. Paris-Sud, Fac. de médecine-UVSQ, INSERM, Université Paris-Saclay, Villejuif, France. [9]Gustave Roussy, Villejuif, France. [10]Hellenic Health Foundation, Athens, Greece. [11]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy. [12]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [13]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway. [14]Public Health División of Gipuzkoa, BioDonostia Research Institute, San-Sebastian-Donostia, Spain. [15]CIBER Epidemiología y Salud Pública, Madrid, Spain. [16]Department of Clinical Sciences, Obstetrics and Gynecology, Umeå University, Umeå, Sweden. [17]Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. [18]International Agency for Research on Cancer, Lyon, France. [19]Division of Pediatric Epidemiology and Clinical Research, University of Minnesota, Minneapolis, Minnesota. [20]Department of Exercise and Nutrition Sciences, Milken Institute School of Public Health, George Washington University, Washington, DC. [21]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia. [22]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. [23]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. [24]University of Southern California, Los Angeles, California. [25]Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii. [26]Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands. [27]New York University School of Medicine, New York, New York. [28]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, Durham, North Carolina. [29]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [30]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. [31]Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington. [32]Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington. [33]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Washington, DC. [34]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida. [35]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

S.S. Tworoger and L.J. Schouten contributed equally to this article and are co-last authors of this article.

Corresponding Authors: Renée T. Fortner, Deutsches Krebsforschungszentrum (DKFZ), Im Neuenheimer Feld 280, Heidelberg 69120, Germany. Phone: 49 6221 42 2241; E-mail: r.fortner@dkfz-heidelberg.de; and Leo J. Schouten, lj.schouten@maastrichtuniversity.nl

Cancer Epidemiol Biomarkers Prev 2020;29:2010–8

doi: 10.1158/1055-9965.EPI-20-0354

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

Introduction

Epithelial ovarian cancer is often investigated as a composite outcome including ovarian, primary peritoneal, and fallopian tube cases, given commonalities (e.g., histologic subtypes, pathologic staging) and potentially shared tissues of origin (e.g., serous tumors predominantly from the fallopian tube, endometrioid, and clear cell from endometriosis and endometrioid adenofibromas; ref. 1). Relatively few studies have investigated risk factors by primary anatomic site (2–10). To date, these studies have suggested potential heterogeneity in associations by primary site for pregnancy-related and anthropometric characteristics, hysterectomy, and family history of cancer. Prospective studies (3, 7) are sparse given the relative rarity of cancers diagnosed as fallopian tube or primary peritoneal cancer [e.g., incidence of ovarian, fallopian tube, and primary peritoneal cancers are estimated at 6.6 per 100,000, 0.62 per million, and 6.78 per million women per year, respectively (5, 11, 12)].

Given the limited evidence to date, the aim of this study was to evaluate whether the association between risk factors for invasive epithelial cancers arising in the peritoneal cavity differ by anatomic site at diagnosis (i.e., ovarian, primary peritoneal, fallopian tube), and, if differences were observed, to investigate whether these differences persist after restriction to (high-grade) serous tumors, given recognized heterogeneity in risk factors by histologic subtype (13). This study was conducted using the Ovarian Cancer Cohort Consortium (OC3), including 3,738 ovarian, 337 primary peritoneal, and 176 fallopian tube incident cancer cases accrued from approximately 892,000 women in 15 prospective cohorts.

Materials and Methods

Study sample

This analysis included women from 15 of the prospective cohorts participating in the OC3 (Supplementary Table S1; ref. 13). OC3 cohorts were required to have: (i) prospective follow-up for incident ovarian cancer diagnoses and deaths and (ii) information on age at recruitment, oral contraceptive (OC) use, and parity. For this study, information on incident peritoneal and fallopian tube cancer cases was also required. All participating studies received institutional approval for cohort data collection and follow-up and the OC3 data coordinating center and analytic approaches were approved by the institutional review board of the Brigham and Women's Hospital.

Risk factors

Data from baseline questionnaires for 14 full cohorts and one case–cohort study with weights were centrally harmonized. Risk factors selected for this study were known and putative ovarian cancer risk factors, with data available and centrally harmonized for the OC3.

Exposures in this analysis were: age at menarche (continuous, per 2 years), OC use (never, ever; continuous duration, per 5 years for ever users), parity (nulliparous, one or more pregnancies; continuous for each additional pregnancy), age at first birth (continuous, per 5 years in parous women), age at last birth (continuous, per 5 years in parous women), duration of breastfeeding (continuous, per 6 months in parous women), hysterectomy (never, ever), unilateral oophorectomy (never, ever), tubal ligation (never, ever), menopausal status (premenopausal, postmenopausal), age at menopause (continuous, per 2 years in postmenopausal women), duration of menopausal hormone therapy (MHT; never, ever; continuous, per 5 years in MHT users), height (continuous, per 5 cm), body mass index (BMI) at ages 18–21 (continuous, per 5 kg/m^2), BMI at baseline (continuous, per 5 kg/m^2), family history of breast cancer (no, yes), family history of ovarian cancer (no, yes), and smoking status (ever, never). If a study did not collect information on a specific exposure, that study was excluded from the analysis of that factor (Supplementary Table S2).

Ovarian, primary peritoneal, and fallopian tube cancer

Cases of epithelial ovarian, primary peritoneal, and fallopian tube cancer were confirmed through medical record review or through cancer registries (13). When using cancer registry data, cases were classified by ICD-O-3/ICD-10 (ovary: C56.9; fallopian tube: C57.0, C57.4; peritoneum: C48.1, C48.2, C48.8, C57.1) or ICD-O-1/ICD-9 (ovary: 183.0; fallopian tube: 183.2, 183.8, 183.9; peritoneum: 158.8, 158.9, 183.3) codes. Cases based on medical record review were generally classified on the basis of pathologist expert opinion; during the timeframe of case ascertainment (1980–2015), this was based on the anatomic site of the dominant mass.

Statistical methods

Women with a personal history of cancer (except nonmelanoma skin cancer) at baseline or bilateral oophorectomy were excluded. We used competing-risks Cox proportional hazards regression to estimate HRs and 95% confidence intervals (CI) for the associations between the selected exposures and risk of ovarian cancer, peritoneal cancer, and fallopian tube cancers (14). Participants were censored at the date of ovarian, peritoneal, or fallopian tube cancer diagnosis, death, or end of follow-up, whichever came first. A Kolmogorov-type supremum test indicated no evidence of violation of the proportional hazards assumption, with the exception for the associations between height and all fallopian tube cancers and between BMI and serous ovarian cancer. Data from the 15 cohorts were pooled and all analyses were stratified by cohort and year of birth to allow for baseline hazards to vary by these factors; no statistically significant heterogeneity was observed in random effects meta-analysis. A priori, all models were adjusted for age at study entry, parity, number of pregnancies beyond the first, and duration of OC use; hysterectomy analyses were also adjusted for MHT use duration. To assess heterogeneity of associations by tumor site, we used likelihood ratio tests to compare a model that allowed the association for the risk factor of interest to vary by tumor site with one that did not (14). Missing indicators were included in the model for any missing data in covariates (parity, 2.6% missing; duration OC use, 2.0% missing). The Sister Study was excluded from analyses of family history because all participants had a family history of breast cancer. We examined the associations between the risk factors and invasive ovarian, peritoneal, and fallopian tube cancers overall, and restricted to known serous or high-grade serous tumors. We used SAS 9.4 software (SAS Institute) to conduct the analyses and $P < 0.05$ was considered statistically significant.

Availability of data and material

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php. For information on data access for the OC3, please see the instructions at: http://theoc3.org/policies/.

Results

From the 891,731 participants (951,538 with the inclusion of full cohort for the case–cohort study), we identified 3,738 incident invasive

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

cases with the ovary as the primary anatomic site, 337 invasive primary peritoneal cancer cases, and 176 invasive fallopian tube cancer cases (**Table 1**). For tumors with known histology ($n = 3{,}487$, 82%), serous was the most common histotype (ovarian = 56.9%, fallopian tube = 71.8%, primary peritoneal = 50.0%).

Reproductive and hormonal factors

Of the examined reproductive and hormonal risk factors, first pregnancy ($P_{het} = 0.04$) and tubal ligation ($P_{het} = 0.01$) were differentially associated with risk of ovarian and primary peritoneal cancers overall (**Table 2**; all other $P_{het} \geq 0.15$). First pregnancy and tubal

Table 1. Selected characteristics of study participants at baseline by case status and primary anatomic site at diagnosis: OC3.

	Noncases (*N* = 887,480)	Ovarian cancer (*N* = 3,738)	Peritoneal cancer (*N* = 337)	Fallopian tube cancer (*N* = 176)
Means (SD)				
Age at recruitment (years)	52.3 (12.2)	57.9 (10.0)	59.2 (9.7)	57.5 (9.7)
Height (cm)	163.2 (6.7)	163.8 (6.6)	164.6 (6.0)	164.0 (6.2)
BMI at age 18 (kg/m^2)	21.1 (3.1)	21.1 (2.9)	21.5 (3.3)	20.8 (2.3)
Current BMI (kg/m^2)	25.6 (5.1)	25.7 (5)	26.5 (6)	26.2 (5)
Age at menarche (years)	12.7 (1.5)	12.8 (1.6)	12.7 (1.6)	12.7 (1.6)
OC use among ever users (years)	5.7 (5.8)	4.8 (5.1)	4.7 (5.2)	5.1 (4.5)
Parity[a]	2.7 (1.4)	2.8 (1.4)	2.9 (1.4)	2.8 (1.6)
Age at first birth (years)[a]	24.7 (4.3)	24.9 (4.3)	24.7 (4.1)	24.7 (4.4)
Age at last birth (years)[a]	30 (4.8)	30.4 (4.7)	30.5 (4.7)	30.1 (5)
Breastfeeding (months)[b]	10.1 (12.5)	8.4 (11.1)	8.5 (12.3)	7 (7.7)
Age at menopause (years)[c]	49.2 (5.1)	49.5 (4.9)	49.8 (4.7)	50.1 (4.1)
Duration MHT use (years)[c]	2.7 (4.7)	3.1 (5.5)	3.7 (5.7)	4.4 (6)
Year of diagnosis		1999.6 (6.4)	2001.7 (5.5)	2002.2 (4.8)
Percent				
Ever OC user	59.5	41.3	45.6	46.2
Parous	85.4	83.9	88.8	90.2
Family history of breast cancer[d]	8.1	11.5	9.9	14.7
Family history of ovarian cancer[d]	2.3	3.2	3.5	5.0
Hysterectomy	13.1	16.5	18.5	14.9
Unilateral oophorectomy	4.5	3.5	5.6	4.5
Tubal ligation	12.5	8.0	14.6	10.1
Ever smoker	42.3	43.3	42.5	48.0
Postmenopausal	59.2	79.5	84.7	78.6
Ever MHT use	48.9	48.0	50.2	56.2
Histology				
Serous		56.9	71.8	50.0
Endometrioid		11.5	0.6	5.7
Mucinous		6.0	1.8	1.1
Clear cell		5.2	0.0	0.6
Poorly differentiated		3.9	1.2	5.7
Unknown		1.5	24.6	36.9
Stage				
1 (Localized)		16.1	3.0	23.3
2 (Regional)		17.9	9.2	19.3
3 (Distant)		54.4	55.5	42.6
Unknown		11.6	32.3	14.8
Grade				
Well-differentiated		6.0	2.7	2.3
Moderately differentiated		15.4	7.7	9.7
Poorly differentiated		38.6	27.6	40.3
Undifferentiated		3.6	5.9	5.1
Unknown		36.4	56.5	42.6
Source of case confirmation[e]				
Medical record		48.9	53.1	58.0
Cancer registry		51.1	46.9	42.0

[a]Among parous.
[b]Among ever breastfed.
[c]Among postmenopausal.
[d]Sisters study excluded as all participants have family history of breast cancer.
[e]Unknown source of case confirmation for 13.8% (ovarian), 19.0% (primary peritoneal), and 14.8% (fallopian tube). Number of missing observations: age at menarche ($N = 13{,}546$), height ($N = 50{,}791$), BMI at age 18 ($N = 427{,}843$), BMI ($N = 60{,}761$), oral contraceptive use ($N = 18{,}211$), parity ($N = 23{,}099$), age at first birth among parous ($N = 44{,}135$), age at last birth ($N = 238{,}242$), duration of breastfeeding ($N = 374{,}116$), tubal ligation ($N = 64{,}111$), hysterectomy ($N = 9{,}982$), smoking status ($N = 9{,}101$), family history of breast cancer ($N = 60{,}044$), family history of ovarian cancer ($N = 370{,}709$), menopausal status ($N = 56{,}450$), age at menopause ($N = 90{,}062$), duration of MHT use ($N = 24{,}340$).

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

Table 2. HRs and 95% CIs between selected reproductive and hormonal factors and ovarian, peritoneal, and fallopian tube cancer: OC3.

	Ovarian cancer HR (95% CI)	Peritoneal cancer HR (95% CI)	Fallopian tube cancer HR (95% CI)	Ovarian vs. peritoneal P_{het}	Ovarian vs. fallopian tube P_{het}	Peritoneal vs. fallopian tube P_{het}
Age at menarche (per 2 years)						
All	(*N* = 3,662)	(*N* = 334)	(*N* = 174)	0.92	0.54	0.65
	0.96 (0.92–1.00)	0.96 (0.83–1.11)	1.02 (0.84–1.24)			
Serous only	(*N* = 2,089)	(*N* = 239)	(*N* = 87)	0.95	0.55	0.62
	0.97 (0.92–1.03)	0.96 (0.82–1.14)	0.88 (0.68–1.13)			
OC use (ever vs. never)						
All	(*N* = 3,665)	(*N* = 331)	(*N* = 173)	0.17	0.54	0.76
	0.84 (0.77–0.90)	0.96 (0.76–1.26)	0.91 (0.65–1.27)			
Serous only	(*N* = 2,089)	(*N* = 237)	(*N* = 87)	0.32	0.90	0.52
	0.82 (0.74–0.91)	0.95 (0.70–1.28)	0.76 (0.48–1.21)			
OC use among ever users (per 5 years)						
All	(*N* = 1,488)	(*N* = 150)	(*N* = 80)	0.89	0.75	0.73
	0.88 (0.84–0.93)	0.86 (0.72–1.03)	0.91 (0.75–1.12)			
Serous only	(*N* = 844)	(*N* = 111)	(*N* = 32)	0.93	0.27	0.32
	0.87 (0.82–0.93)	0.85 (0.68–1.07)	1.07 (0.82–1.39)			
Parity						
All	(*N* = 3,629)	(*N* = 329)	(*N* = 173)			
First pregnancy	**0.81 (0.73–0.90)**	1.15 (0.78–1.70)	1.43 (0.80–2.55)	**0.04**	0.08	0.81
Per additional pregnancy	**0.93 (0.90–0.95)**	0.92 (0.85–1.00)	0.86 (0.73–1.01)	0.42	0.75	0.46
Serous only	(*N* = 2,067)	(*N* = 236)	(*N* = 86)			
First pregnancy	0.90 (0.78–1.04)	1.25 (0.78–2.03)	**3.52 (1.02–12.1)**	0.23	**0.02**	0.11
Per additional pregnancy	**0.95 (0.92–0.98)**	0.92 (0.84–1.01)	0.84 (0.66–1.09)	0.93	0.72	0.78
Age at first birth[a] (per 5 years)						
All	(*N* = 2,931)	(*N* = 280)	(*N* = 147)	0.84	0.89	0.99
	0.99 (0.95–1.04)	1.01 (0.87–1.17)	0.94 (0.76–1.18)			
Serous only	(*N* = 1,727)	(*N* = 205)	(*N* = 77)	0.53	0.77	0.55
	0.98 (0.92–1.04)	1.02 (0.86–1.21)	0.84 (0.63–1.13)			
Age at last birth[a] (per 5 years)						
All	(*N* = 1,565)	(*N* = 137)	(*N* = 75)	0.80	0.44	0.63
	0.98 (0.93–1.04)	0.93 (0.75–1.16)	0.94 (0.72–1.22)			
Serous only	(*N* = 960)	(*N* = 115)	(*N* = 41)	0.94	0.07	0.13
	0.98 (0.91–1.05)	0.95 (0.76–1.19)	0.79 (0.56–1.13)			
Breastfeeding[a] (per 6 months)						
All	(*N* = 997)	(*N* = 99)	(*N* = 51)	0.56	0.19	0.15
	0.97 (0.93–1.01)	1.01 (0.90–1.13)	0.86 (0.72–1.02)			
Serous only	(*N* = 611)	(*N* = 84)	(*N* = 21)	0.29	0.33	0.17
	0.96 (0.92–1.01)	1.04 (0.92–1.17)	0.89 (0.71–1.12)			
Hysterectomy[b]						
All	(*N* = 3,689)	(*N* = 335)	(*N* = 175)	0.78	0.24	0.42
	0.94 (0.86–1.03)	0.91 (0.67–1.23)	**0.65 (0.42–0.98)**			
Serous only	(*N* = 2,105)	(*N* = 240)	(*N* = 87)	0.11	**0.02**	0.20
	1.00 (0.89–1.13)	0.77 (0.53–1.12)	**0.46 (0.23–0.90)**			
Unilateral oophorectomy						
All	(*N* = 3,738)	(*N* = 337)	(*N* = 176)	0.15	0.49	0.79
	0.63 (0.53–0.75)	0.93 (0.58–1.49)	0.83 (0.40–1.70)			
Serous only	(*N* = 2,127)	(*N* = 242)	(*N* = 88)	0.34	0.48	0.92
	0.52 (0.41–0.67)	0.73 (0.40–1.35)	0.79 (0.28–2.22)			
Tubal ligation						
All	(*N* = 3,331)	(*N* = 302)	(*N* = 148)	**0.01**	0.99	0.11
	0.82 (0.71–0.93)	1.31 (0.93–1.84)	0.78 (0.45–1.37)			
Serous only	(*N* = 1,884)	(*N* = 214)	(*N* = 69)	**0.02**	0.86	0.20
	0.85 (0.72–1.01)	1.42 (0.97–2.06)	0.77 (0.33–1.82)			
Postmenopausal status						
All	(*N* = 3,606)	(*N* = 326)	(*N* = 168)	0.84	0.94	0.94
	0.96 (0.81–1.15)	1.05 (0.58–1.91)	0.99 (0.55–1.80)			
Serous only	(*N* = 2,035)	(*N* = 233)	(*N* = 84)	0.55	0.89	0.79
	0.97 (0.77–1.22)	1.26 (0.60–2.67)	1.08 (0.50–2.33)			

(Continued on the following page)

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

Table 2. HRs and 95% CIs between selected reproductive and hormonal factors and ovarian, peritoneal, and fallopian tube cancer: OC3. (Cont'd)

	Ovarian cancer HR (95% CI)	Peritoneal cancer HR (95% CI)	Fallopian tube cancer HR (95% CI)	Ovarian vs. peritoneal P_{het}	Ovarian vs. fallopian tube P_{het}	Peritoneal vs. fallopian tube P_{het}
Age at menopause[c] (per 2 year increase)						
All	(*N* = 2,371)	(*N* = 236)	(*N* = 107)	0.66	0.34	0.58
	1.03 (1.01–1.04)	1.04 (0.98–1.09)	1.07 (0.99–1.15)			
Serous only	(*N* = 1,368)	(*N* = 164)	(*N* = 63)	0.43	0.33	0.68
	1.03 (1.01–1.05)	1.06 (0.99–1.13)	1.09 (0.98–1.20)			
MHT use (ever vs. never)[c]						
All	(*N* = 2,789)	(*N* = 271)	(*N* = 130)	0.21	0.26	0.09
	1.29 (1.19–1.39)	1.07 (0.83–1.38)	**1.56 (1.07–2.28)**			
Serous only	(*N* = 1,621)	(*N* = 190)	(*N* = 70)	0.15	0.72	0.66
	1.34 (1.21–1.49)	1.05 (0.78–1.43)	1.17 (0.70–1.96)			
Duration MHT use[c] (per 5 years)						
All	(*N* = 2,679)	(*N* = 259)	(*N* = 124)	0.47	0.26	0.17
	1.22 (1.17–1.27)	**1.16 (1.04–1.30)**	**1.33 (1.14–1.56)**			
Serous only	(*N* = 1,564)	(*N* = 183)	(*N* = 68)	0.18	0.30	0.78
	1.28 (1.22–1.34)	**1.15 (1.01–1.32)**	1.08 (0.83–1.40)			

Note: Adjusted for age, study, birth year, parity [ever parous (binary) and number of additional pregnancies], oral contraceptive use duration (continuous). Bold type indicates a statistically significant hazard ratio (HR) or *P* for heterogeneity (P_{het}).
[a]Among parous women.
[b]Additionally adjusted for duration of MHT use.
[c]Among postmenopausal women.

ligation were inversely associated with risk of tumors with the primary anatomic site at the ovary [first pregnancy compared with nulliparous, HR = 0.81 (0.73–0.90); tubal ligation, 0.82 (0.71–0.93)], while no evidence of an inverse association was observed for primary peritoneal cancers [first pregnancy, 1.15 (0.78–1.70); tubal ligation, 1.31 (0.93–1.84)]. Results were similar for serous cases. We observed no statistically significant heterogeneity for any reproductive risk factor comparing ovarian with fallopian cancers, but in analyses restricted to serous cancers, heterogeneity of associations was observed for first pregnancy and hysterectomy (both $P = 0.02$). First pregnancy was associated with higher risk of serous fallopian tube cancer [3.52 (1.02–12.1)], but not serous ovarian cancer [0.90 (0.78–1.04)]; in further analyses, parity of 1 versus nulliparity was suggestively associated with serous fallopian tube cancer [1.64 (0.88–3.09)], and significantly inversely associated with ovarian cancer [0.81 (0.68–0.97)] (data not tabled). Hysterectomy was inversely associated with serous fallopian tube [0.46 (0.23–0.90)], but not ovarian [1.00 (0.89–1.13)], cancers. We observed no heterogeneity in associations comparing fallopian tube with primary peritoneal cancers for all cases ($P_{het} \geq 0.08$) or in analyses restricted to serous cases; though the sample size in these subgroups was limited. Other risk factors were similarly associated with risk of the three endpoints.

When restricting to cases with the high-grade serous histotype, the patterns of associations were generally similar to those observed for all histotypes or the serous histotype (Supplementary Table S3). We further observed significant heterogeneity for OC use with risk of ovarian and primary peritoneal cancers ($P = 0.02$) and age at first and last birth (both $P = 0.02$) with risk of high-grade serous fallopian tube and primary peritoneal cancers. Specifically, ever OC use (relative to never) was significantly inversely associated with ovarian [0.82 (0.73–0.93)], but not associated with primary peritoneal cancers [1.48 (0.92–2.38)]. Older age at first birth was positively associated with high-grade serous primary peritoneal cancer [per 5 years, HR = 1.30 (1.04–1.62)], but not high-grade serous fallopian tube cancer [0.72 (0.49–1.05)]; a similar pattern was observed for age at last birth.

Anthropometric, family history, and lifestyle risk factors

The association between early adult (ages 18–21) BMI and, for serous tumors, baseline BMI differed by anatomic site (**Table 3**). Higher early-adult BMI was positively associated with risk of peritoneal cancer [per 5 kg/m^2, HR = 1.29 (1.07–1.57)], but not ovarian [$P_{het} = 0.02$; 0.99 (0.92–1.06)] or fallopian tube [$P_{het} = 0.03$; 0.85 (0.64–1.13)] cancers; results were similar for (high-grade) serous tumors. The associations between baseline BMI and serous ovarian and peritoneal cancer were significantly different ($P_{het} = 0.01$), with a suggestively lower risk of serous ovarian and suggestively higher risk of primary peritoneal cancer [per 5 kg/m^2, ovarian, 0.96 (0.92–1.01); primary peritoneal, 1.14 (0.99–1.30)]. When cases were restricted to high-grade serous tumors, additional heterogeneity in associations between height (P_{het}<0.01) and family history of breast cancer ($P_{het} = 0.03$) and ovarian and primary peritoneal cancers was observed (Supplementary Table S4). Taller height was more strongly associated with high-grade serous primary peritoneal disease [per 5 cm, HR = 1.30 (1.15–1.47)] than ovarian [HR = 1.04 (1.00–1.09)]. Family history of breast cancer was associated with high-grade serous ovarian cancer [HR = 1.25 (1.06–1.48)], but not primary peritoneal cancer [HR = 0.58 (0.27–1.26)].

Discussion

In our prospective analysis of >890,000 women, selected reproductive factors, body size, and family history displayed variability in associations for ovarian, peritoneal, and fallopian tube cancers; however, the majority of exposures were similarly associated with risk regardless of anatomic site within the peritoneal cavity. Understanding of the tissue(s) of origin of primary ovarian, fallopian, and peritoneal cancers have evolved rapidly, with hypothesized shared tissue of origin for cancers at these sites, particularly for high-grade serous disease arising from the fallopian tube. Overall, our results in which most risk factors were associated similarly across anatomic sites supports this hypothesis, although select risk factors may have differential influence on the primary tissues on which tumors present.

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

Table 3. HRs and 95% CIs between selected anthropometric, family history, and lifestyle factors and ovarian, peritoneal, and fallopian tube cancer: OC3.

	Ovarian cancer HR (95% CI)	Peritoneal cancer HR (95% CI)	Fallopian tube cancer HR (95% CI)	P_{het} (ovarian vs. peritoneal)	P_{het} (ovarian vs. fallopian tube)	P_{het} (peritoneal vs. fallopian tube)
Height (per 5 cm)						
All	(*N* = 3,616)	(*N* = 334)	(*N* = 174)	0.06	0.42	0.65
	1.06 (1.04–1.09)	**1.15 (1.07–1.24)**	1.12 (1.00–1.25)[a]			
Serous only	(*N* = 2,045)	(*N* = 241)	(*N* = 88)	0.10	0.06	0.43
	1.06 (1.03–1.10)	**1.16 (1.07–1.27)**	**1.26 (1.09–1.45)**			
BMI at ages 18–21 (per 5 kg/m^2)						
All	(*N* = 2,365)	(*N* = 226)	(*N* = 111)	**0.02**	0.35	**0.03**
	0.99 (0.92–1.06)	**1.29 (1.07–1.57)**	0.85 (0.64–1.13)			
Serous only	(*N* = 1,275)	(*N* = 177)	(*N* = 50)	**0.01**	0.80	0.33
	0.96 (0.88–1.06)	**1.33 (1.08–1.64)**	1.11 (0.78–1.58)			
Current (baseline) BMI (per 5 kg/m^2)						
All	(*N* = 3,564)	(*N* = 331)	(*N* = 173)	0.08	0.66	0.49
	1.01 (0.98–1.05)	1.12 (1.00–1.26)	1.06 (0.92–1.23)			
Serous only	(*N* = 2,021)	(*N* = 238)	(*N* = 87)	**0.01**	0.25	0.78
	0.96 (0.92–1.01)[a]	1.14 (0.99–1.30)	1.12 (0.90–1.38)			
Family history of breast cancer						
All	(*N* = 3,617)	(*N* = 324)	(*N* = 163)	0.10	0.55	0.13
	1.19 (1.07–1.32)	0.87 (0.60–1.26)	1.36 (0.86–2.16)			
Serous only	(*N* = 2,059)	(*N* = 232)	(*N* = 81)	0.16	0.78	0.32
	1.19 (1.03–1.36)	0.86 (0.56–1.33)	1.28 (0.66–2.50)			
Family history of ovarian cancer						
All	(*N* = 2,704)	(*N* = 282)	(*N* = 139)	0.94	0.42	0.48
	1.67 (1.34–2.07)	1.62 (0.86–3.07)	**2.32 (1.07–5.02)**			
Serous only	(*N* = 1,465)	(*N* = 214)	(*N* = 64)	0.97	0.81	0.81
	1.82 (1.39–2.40)	1.85 (0.94–3.63)	1.49 (0.36–6.10)			
Smoking status (ever vs. never)						
All	(*N* = 3,696)	(*N* = 334)	(*N* = 175)	0.61	0.12	0.11
	1.02 (0.95–1.09)	0.96 (0.77–1.19)	1.31 (0.95–1.80)			
Serous only	(*N* = 2,099)	(*N* = 240)	(*N* = 87)	0.70	0.15	0.14
	1.04 (0.95–1.14)	0.98 (0.76–1.27)	1.44 (0.90–2.30)			

Note: Adjusted for age, study, birth year, parity [ever parous (binary) and number of additional pregnancies], oral contraceptive use duration (continuous). Bold type indicates a statistically significant hazard ratio (HR) or *P* for heterogeneity (P_{het}).

[a]Proportional hazards assumption violated in model evaluating association between height and fallopian tube cancers (all cases) and BMI and serous ovarian cancer.

Tubal ligation was inversely associated with ovarian cancer (18% lower risk) but not with fallopian tube and primary peritoneal cancer. Previous studies have shown consistent associations to our study (5–7, 13, 15). Studies have evaluated risk factors by tumor dominance as a proxy for ovarian or tubal origin (16, 17), including one in the OC3 [17; i.e., dominant mass corresponding to tumor of ovarian origin and nondominant mass corresponding to tumor of tubal origin (18)], and observed significant inverse associations between tubal ligation and risk only for dominant tumors, in line with our findings. Mechanistically, tubal ligation is thought to prevent primarily endometrioid, clear cell, and low-grade serous tumors by blocking the transit of precursor cells from the endometrium. Consistent with this, we only identified a differential association when examining all histotypes or serous only, but not when restricting to high-grade serous disease.

Hysterectomy was inversely associated with serous fallopian tube cancer (all cases: 35% lower risk; serous cases: 54% lower risk), but not serous ovarian or peritoneal cancer. Case–control studies have reported positive associations with risk of ovarian cancer (5, 6), but not primary peritoneal (5) or fallopian tube (6, 7) cancers for women reporting hysterectomy, while a case-only study reported no differential associations by site (3). Fallopian tube cancers are thought to arise predominantly from serous tubal intraepithelial carcinomas (STIC), and a proportion of women undergoing hysterectomy would have had concurrent salpingectomy. Our findings may, at least in part, be an artifact of concurrent unilateral or bilateral salpingectomy.

In general, the first pregnancy was more inversely associated with risk of ovarian cancer than the other types. In fact, we observed a positive association for serous fallopian tube cancer, which is inconsistent with the one other study that reported inverse associations with first pregnancy for both dominant (ovarian) and nondominant (tubal) tumors (16). This finding with serous fallopian tube cancers is likely due to chance. However, the generally stronger inverse relationship of being parous being inversely associated with risk of ovarian cancer is in line with most previous studies of ovarian (13, 19) and fallopian tube (4, 6, 7) cancers; a positive association with risk of primary peritoneal, relative to ovarian, cancer was reported in a case-only analysis (3). Given that the association for subsequent pregnancies (after the first) were very similar across anatomic sites, it seems unlikely that there is a strong differential relationship by parity.

We observed heterogeneity in associations for early-adult and baseline BMI (for serous only), and height (for high-grade serous only). While taller height was positively associated with risk for all

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

cancer subtypes (4%–30% increased risk per 5 cm), associations were stronger for peritoneal and fallopian tube cancers, suggesting a role for growth factors and earlier life exposures (e.g., energy restriction) for these tumor types. BMI, either in early adulthood or in adulthood, was positively associated solely with peritoneal cancer risk. Few studies have examined early adult BMI and risk by ovarian tumor subsite, although a recent study observed that BMI increase from age 10 to 18 years was positively associated with risk of ovarian/primary peritoneal cancer combined, although the association was suggestively stronger among cases of nonserous disease (20). Adult BMI is not a strong risk factor for ovarian cancer, with modest associations observed for the mucinous and endometrioid subtypes (13, 21). Previous studies have suggested no association of adult BMI with fallopian tube cancers (4, 16) and positive associations for primary peritoneal cancers (6, 9). Obesity is a state of chronic low-grade inflammation (22), both systemically and at the local tissue level [i.e., in the visceral (omental) adipose tissue], and inflammation is associated with ovarian cancer risk (23–25). Furthermore, adipose tissue is the predominant source of estrogens in obese postmenopausal women (26), and sex steroid hormones are associated with higher risk of nonserous ovarian cancer (27–29). Finally, ovarian cancer frequently metastasizes to the adipose tissue–rich omentum with immune cell aggregates (so-called "milky clusters") within this adipose tissue acting in immune modulation and identified as sites of metastatic colonization (30). Given that primary peritoneal cancers develop more proximal to the omentum, relative to ovarian and fallopian tube cancers, an inflammatory and sex steroid hormone–rich tumor microenvironment, together with omental adipose tissue–related promotion of metastases, represent plausible mechanisms linking BMI more strongly with primary peritoneal cancers.

A limitation of this study is potential misclassification of primary peritoneal and fallopian tube cancers as primary ovarian cancer because the classification of these is largely based on a subjective determination of disease spread at the time of surgery and registry-based cases were categorized on the basis of the coding rules used by cancer registries. Nonetheless, despite potential misclassification, differences in risk associations by anatomic site for selected risk factors have generally been consistent across studies. Pathology protocols including detailed pathologic evaluation of the fallopian tubes (i.e., the SEE-FIM protocol) and greater awareness of and surveillance for STICs contribute to improved classification of anatomic site at diagnosis, and likely account for the recent increase in diagnosed fallopian tube cancers (e.g., 16.2% annual percentage change from 2002 to 2012 in the United States; ref. 12). These relatively recent advances will provide improved classification with respect to site of origin (rather than progression) for future prospective studies. Future studies may also consider risk factors beyond those included in the present analysis (e.g., antiinflammatory analgesic use).

Overall, our findings suggest that tumors identified as ovarian, primary peritoneal, and fallopian tube cancers have both shared and distinct etiologic pathways, although most risk factors appear to have similar associations by anatomic site. This is in contrast to previous investigations by histotype (13), which is likely to be more reflective of the cell of origin than the anatomic location of tumor presentation. The risk factors that did differ, particularly adiposity measures, suggest that these exposures may be important for determining the vulnerability of the anatomic site to tumor growth. Patterns were generally similar in analyses restricted to (high-grade) serous cancers, suggesting that the heterogeneity in associations was not explained by histotype. Enhanced understanding of these differential risk patterns, and mechanistic studies toward a more refined understanding of the underlying physiologic processes leading to this heterogeneity, may inform prevention efforts for these cancers.

Disclosure of Potential Conflicts of Interest

M.S. Rice reports employment with Sanofi (all work on this manuscript was completed prior to her employment with Sanofi). M.J. Orlich reports grants from NCI and World Cancer Research Fund during the conduct of the study. J.N. Poynter reports grants from NIH during the conduct of the study. K. Robien reports grants from NIH/NCI R01 CA39742 during the conduct of the study. G.G. Giles reports grants from National Health and Medical Research Council (to institution, Cancer Council Victoria) during the conduct of the study. R.L. Milne reports grants from National Health and Medical Research Council during the conduct of the study. V.W. Setiawan reports grants from NIH during the conduct of the study. A. Zeleniuch-Jacquotte reports grants from NIH/NCI during the conduct of the study. A. Wolk reports grants from The Swedish Cancer Foundation and The Swedish Research Council/SIMPLER during the conduct of the study. S.S. Tworoger reports grants from U.S. Department of Defense and NCI during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Authors' Contributions

R.T. Fortner: Conceptualization, resources, formal analysis, supervision, investigation, writing–original draft, writing–review and editing. **M.S. Rice:** Conceptualization, data curation, formal analysis, investigation, writing–original draft, project administration, writing–review and editing. **S.F. Knutsen:** Resources, investigation, writing–review and editing. **M.J. Orlich:** Resources, investigation, writing–review and editing. **K. Visvanathan:** Resources, investigation, writing–review and editing. **A.V. Patel:** Resources, investigation, writing–review and editing. **M.M. Gaudet:** Resources, investigation, writing–review and editing. **A. Tjønneland:** Resources, investigation, writing–review and editing. **M. Kvaskoff:** Resources, investigation, writing–review and editing. **R. Kaaks:** Resources, investigation, writing–review and editing. **A. Trichopoulou:** Resources, investigation, writing–review and editing. **V. Pala:** Resources, investigation, writing–review and editing. **N.C. Onland-Moret:** Resources, investigation, writing–review and editing. **I.T. Gram:** Resources, investigation, writing–review and editing. **P. Amiano:** Resources, investigation, writing–review and editing. **A. Idahl:** Resources, investigation, writing–review and editing. **N.E. Allen:** Resources, investigation, writing–review and editing. **E. Weiderpass:** Resources, investigation, writing–review and editing. **J.N. Poynter:** Resources, investigation, writing–review and editing. **K. Robien:** Resources, investigation, writing–review and editing. **G.G. Giles:** Resources, investigation, project administration. **R.L. Milne:** Resources, investigation, writing–review and editing. **V.W. Setiawan:** Resources, investigation, writing–review and editing. **M.A. Merritt:** Resources, investigation, writing–review and editing. **P.A. van den Brandt:** Resources, investigation, writing–review and editing. **A. Zeleniuch-Jacquotte:** Resources, investigation, writing–review and editing. **A.A. Arslan:** Resources, investigation, writing–review and editing. **K.M. O'Brien:** Resources, investigation, writing–review and editing. **D.P. Sandler:** Resources, investigation, writing–review and editing. **A. Wolk:** Resources, investigation, project administration. **N. Håkansson:** Resources, investigation, writing–review and editing. **H.R. Harris:** Resources, investigation, writing–review and editing. **B. Trabert:** Resources, investigation, writing–review and editing. **N. Wentzensen:** Resources, investigation, writing–review and editing. **S.S. Tworoger:** Conceptualization, resources, supervision, funding acquisition, investigation, project administration, writing–review and editing. **L.J. Schouten:** Conceptualization, resources, supervision, investigation, project administration, writing–review and editing.

Acknowledgments

The authors thank the participants and staff of the participating cohorts for their valuable contributions as well as the following U.S. state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY, the Netherlands Cancer Registry, and the Netherlands Pathology Registry.

Cancer data for some studies were provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, with funding from the State of Maryland and the Maryland Cigarette Restitution Fund. The collection and availability of cancer registry data are also supported by Cooperative Agreement NU58DP006333, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Supported by Department of Defense Ovarian Cancer Research Program grant W81XWH-12-1-0561 (PI: to S.S. Tworger). Also supported by K05 CA154337 from the NCI and Office of Dietary Supplements [VITAL (Vitamins and Lifestyle study cohort)]; R01 CA39742 (Iowa Women's Health Study); CA164973 (Multiethnic Cohort); UM1 CA186107, P01 CA87969, UM1 CA176726, and R01 CA67262 (Nurses' Health Study, Nurses' Health Study II); NIH UM1 CA182934 and center grants P30 CA016087 and P30 ES000260 (NYU Women's Health Study); grants from the Swedish Research Council (Swedish Mammography Cohort). All aspects of the Cancer Prevention Study II were funded by the Intramural Research Program of the American Cancer Society and by the NCI Intramural Research Program, Intramural Research Program of the NIH, and National Institute of Environmental Health Sciences. The Sister Study is funded by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences project Z01-ES044005. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM; France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF; Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Nordforsk (Norway); Health Research Fund (FIS), PI13/00061 to Granada; PI13/01162 to EPIC-Murcia), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020; Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford; United Kingdom). Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414, and 1074383 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 5, 2020; revised May 13, 2020; accepted July 27, 2020; published first July 30, 2020.

References

1. Karnezis AN, Cho KR, Gilks CB, Pearce CL, Huntsman DG. The disparate origins of ovarian cancers: pathogenesis and prevention strategies. Nat Rev Cancer 2017;17:65–74.
2. Barda G, Menczer J, Chetrit A, Lubin F, Beck D, Piura B, et al. Comparison between primary peritoneal and epithelial ovarian carcinoma: a population-based study. Am J Obstet Gynecol 2004;190:1039–45.
3. Schnack TH, Sorensen RD, Nedergaard L, Hogdall C. Demographic clinical and prognostic characteristics of primary ovarian, peritoneal and tubal adenocarcinomas of serous histology–a prospective comparative study. Gynecol Oncol 2014;135:278–84.
4. Vicus D, Finch A, Rosen B, Fan I, Bradley L, Cass I, et al. Risk factors for carcinoma of the fallopian tube in women with and without a germline BRCA mutation. Gynecol Oncol 2010;118:155–9.
5. Grant DJ, Moorman PG, Akushevich L, Palmieri RT, Bentley RC, Schildkraut JM. Primary peritoneal and ovarian cancers: an epidemiological comparative analysis. Cancer Causes Control 2010;21:991–8.
6. Jordan SJ, Green AC, Whiteman DC, Moore SP, Bain CJ, Gertig DM, et al. Serous ovarian, fallopian tube and primary peritoneal cancers: a comparative epidemiological analysis. Int J Cancer 2008;122:1598–603.
7. Riska A, Sund R, Pukkala E, Gissler M, Leminen A. Parity, tubal sterilization, hysterectomy and risk of primary fallopian tube carcinoma in Finland, 1975–2004. Int J Cancer 2007;120:1351–4.
8. Eltabbakh GH, Piver MS, Natarajan N, Mettlin CJ. Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. Obstet Gynecol 1998;91:254–9.
9. Olsen CM, Nagle CM, Whiteman DC, Purdie DM, Green AC, Webb PM. Body size and risk of epithelial ovarian and related cancers: a population-based case-control study. Int J Cancer 2008;123:450–6.
10. Halperin R, Zehavi S, Langer R, Hadas E, Bukovsky I, Schneider D. Primary peritoneal serous papillary carcinoma: a new epidemiologic trend? A matched-case comparison with ovarian serous papillary cancer. Int J Gynecol Cancer 2001;11:403–8.
11. Global Cancer Observatory [homepage on the Internet]. Lyon (France): International Agency for Research on Cancer; 2020. Available from: http://gco.iarc.fr/.
12. Trabert B, Coburn SB, Mariani A, Yang HP, Rosenberg PS, Gierach GL, et al. Reported incidence and survival of fallopian tube carcinomas: a population-based analysis from the North American Association of Central Cancer Registries. J Natl Cancer Inst 2018;110:750–7.
13. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. J Clin Oncol 2016;34:2888–98.
14. Wang M, Spiegelman D, Kuchiba A, Lochhead P, Kim S, Chan AT, et al. Statistical methods for studying disease subtype heterogeneity. Stat Med 2016;35:782–800.
15. Sieh W, Salvador S, McGuire V, Weber RP, Terry KL, Rossing MA, et al. Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. Int J Epidemiol 2013;42:579–89.
16. Kotsopoulos J, Terry KL, Poole EM, Rosner B, Murphy MA, Hecht JL, et al. Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. Int J Cancer 2013;133:730–9.
17. Huang T, Townsend MK, Wentzensen N, Trabert B, White E, Arslan AA, et al. Reproductive and hormonal factors and risk of ovarian cancer by tumor dominance: results from the Ovarian Cancer Cohort Consortium (OC3). Cancer Epidemiol Biomarkers Prev 2020;29:200–7.
18. Roh MH, Kindelberger D, Crum CP. Serous tubal intraepithelial carcinoma and the dominant ovarian mass: clues to serous tumor origin? Am J Surg Pathol 2009;33:376–83.
19. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med 2017;14:9–32.
20. Huang T, Tworoger SS, Willett WC, Stampfer MJ, Rosner BA. Associations of early life and adulthood adiposity with risk of epithelial ovarian cancer. Ann Oncol 2019;30:303–9.
21. Collaborative Group on Epidemiological Studies of Ovarian Cancer; Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303–14.
22. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.

Published OnlineFirst July 30, 2020; DOI: 10.1158/1055-9965.EPI-20-0354

23. Trabert B, Pinto L, Hartge P, Kemp T, Black A, Sherman ME, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. Gynecologic Oncol 2014;135:297–304.
24. Ose J, Schock H, Tjønneland A, Hansen L, Overvad K, Dossus L, et al. Inflammatory markers and risk of epithelial ovarian cancer by tumor subtypes: the EPIC cohort. Cancer Epidemiol Biomarkers Prev 2015;24: 951–61.
25. Poole EM, Lee IM, Ridker PM, Buring JE, Hankinson SE, Tworoger SS. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor receptor 2 levels and risk of ovarian cancer. Am J Epidemiol 2013; 178:1256–64.
26. Yen SS, Jaffe RB, Barbieri RL. Reproductive endocrinology. Philadelphia: W.B. Saunders Company; 1999.
27. Trabert B, Brinton LA, Anderson GL, Pfeiffer RM, Falk RT, Strickler HD, et al. Circulating estrogens and postmenopausal ovarian cancer risk in the Women's Health Initiative Observational Study. Cancer Epidemiol Biomarkers Prev 2016; 25:648–56.
28. Ose J, Poole EM, Schock H, Lehtinen M, Arslan AA, Zeleniuch-Jacquotte A, et al. Androgens are differentially associated with ovarian cancer subtypes in the Ovarian Cancer Cohort Consortium. Cancer Res 2017;77:3951–60.
29. Trabert B, Michels KA, Anderson GL, Brinton LA, Falk RT, Geczik AM, et al. Circulating androgens and postmenopausal ovarian cancer risk in the Women's Health Initiative Observational Study. Int J Cancer 2019;145:2051–60.
30. Motohara T, Masuda K, Morotti M, Zheng Y, El-Sahhar S, Chong KY, et al. An evolving story of the metastatic voyage of ovarian cancer cells: cellular and molecular orchestration of the adipose-rich metastatic microenvironment. Oncogene 2019;38:2885–98.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Ovarian Cancer Risk Factor Associations by Primary Anatomic Site: The Ovarian Cancer Cohort Consortium

Renée T. Fortner, Megan S. Rice, Synnove F. Knutsen, et al.

Cancer Epidemiol Biomarkers Prev 2020;29:2010-2018. Published OnlineFirst July 30, 2020.