**The association between socioeconomic status and tumour stage at diagnosis of ovarian cancer: a pooled analysis of 18 case-control studies**

Camilla Præstegaarda, Susanne K. Kjaera,b,Thor S.S. Nielsena, Signe M. Jensenc, Penelope M. Webbd on behalf of the Australian Ovarian Cancer Study Groupe, Christina M. Nagled, Estrid Høgdalla,f, Harvey A. Rischg, Mary Anne Rossingh,i, Jennifer A. Dohertyj, Kristine G. Wicklundh, Marc T. Goodmank,l, Francesmary Modugnom,n,o, Kirsten Moysichp, Roberta B. Nessq, Robert P. Edwardsr, Ellen L. Goodes, Stacey J. Winhamt, Brooke L. Fridleyt, Daniel W. Crameru, Kathryn L.Terryu,v, Joellen M. Schildkrautw,, Andrew Berchuckx, Elisa V. Banderay, Lisa Paddockz,aa, Lambertus A. Kiemeneybb,cc, Leon F. Massugerdd, Nicolas Wentzensenee, Paul Pharoahff, Honglin Songgg, Alice S. Whittemorehh, Valerie McGuirehh, Weiva Siehhh, Joseph Rothsteinhh, Hoda Anton-Culverii, Argyrios Ziogasjj, Usha Menonkk, Simon A. Gaytherll, Susan J. Ramusll, Aleksandra Gentry-Maharajkk, Anna H. Wull, Celeste L. Pearcell,mm, Malcolm C. Pikell,nn, Alice W. Leell, Jenny Chang-Claudeoo and Allan Jensena on behalf of the Ovarian Cancer Association Consortium.

**Affiliations**

1. Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100 Copenhagen, Denmark
2. Department of Gynecology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
3. Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100 Copenhagen, Denmark
4. Population Health Department, QIMR Berghofer Medical Research Institute, 300 Herston Rd, Herston, Queensland 4006 Brisbane, Australia
5. Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia
6. Molecular Unit, Department of Pathology, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark
7. Department of Chronic Disease Epidemiology, Yale School of Public Health, LEPH 413, 60 College Street, New Haven, Connecticut 06510, USA
8. Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, PO Box 19024, Seattle, Washington 98109-1024, USA
9. Department of Epidemiology, University of Washington, PO Box 19024, Seattle, Washington 98109-1024, USA
10. Department of Community and Family Medicine, Section of Biostatistics & Epidemiology, Geisel School of Medicine, Dartmouth College, 1 Medical Center Drive, 7927 Rubin Building, Room 884, Lebanon, Hanover, New Hampshire 03756, USA
11. Cancer Prevention and Control, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Room 1S37, Los Angeles 90048, California, USA
12. Community and Population Health Research Institute, Department of Biomedical Sciences, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Room 1S37, Los Angeles 90048, California, USA
13. Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, University of Pittsburgh School of Medicine, Magee-Womens Hospital, 300 Halket Street (Room #2130), Pittsburgh, Pennsylvania 15222, USA
14. Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Magee-Womens Hospital, 300 Halket Street (Room #2130), Pittsburgh, Pennsylvania 15222, USA
15. Womens Cancer Research Program, Magee-Womens Research Institute and University of Pittsburgh Cancer Institute, Magee-Womens Hospital, 300 Halket Street (Room #2130), Pittsburgh, Pennsylvania 15222, USA
16. Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York 14263, USA
17. The University of Texas, School of Public Health, P.O. Box 20186, Houston, Texas 77225, USA
18. Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Magee-Womens Hospital, 300 Halket Street (Room #2130), Pittsburgh, Pennsylvania 15222, USA
19. Department of Health Science Research, Division of Epidemiology, Mayo Clinic, 200 First Street SW, Charlton 6, Rochester, Minnesota, USA
20. Department of Biostatistics, University of Kansas, 5028B Robinson Building, 3901 Rainbow Blvd, Kansas City, Kansas 66160, USA
21. Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, 221 Longwood Avenue RFB 368, Boston, Massachusetts 02115, USA
22. Department of Epidemiology, Harvard T. H. Chan School of Public Health, 221 Longwood Avenue RFB 368, Boston, Massachusetts 02115, USA
23. Department of Public Health Sciences, School of Medicine, University of Virginia, Box: 800717, Charlottesville, Virginia 22908, USA
24. Department of Obstetrics and Gynecology, Duke University Medical Center, 3079, Durham, North Carolina 27710, USA
25. Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, 195 Little Albany Street, Room 5568, New Brunswick, New Jersey 08903, USA
26. New Jersey State Cancer registry, PO Box 369, Trenton, New Jersey 08625-0369, USA
27. Rutgers School of Public Health, Piscataway, New Jersey, USA
28. Department for Health Evidence, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands
29. Department of Urology, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands
30. Department of Obstetrics and Gynaecology, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands
31. Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Rockville, Maryland 20852, USA
32. Department of Oncology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research laboratory, Wortscauseway, Cambridge, CB1 8RN, United Kingdom
33. Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Wortscauseway, Cambridge, CB1 8RN, United Kingdom
34. Department of Health Research and Policy - Epidemiology, Stanford University School of Medicine, 259 Campus Drive, Stanford, California 94305-5405, USA
35. Department of Epidemiology, University of California Irvine, Center for Cancer Genetics Research & Prevention, School of Medicine, 224 Irvine Hall, Irvine, California 92697-7550, USA
36. Department of Epidemiology, University of California Irvine, 224 Irvine Hall, Irvine, California 92697-7550, USA
37. Women's Cancer, UCL EGA Institute for Women's Health, Maple House 1st Floor, 149 Tottenham Court Road, London W1T 7DN, United Kingdom
38. Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Harlyne Norris Research Tower 1450 Biggy Street, Office 2517G, Los Angeles, California 90033, USA
39. Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, SPH Tower, Office #4642, Ann Arbor, Michigan 48109-2029, USA
40. Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 307 East 63rd Street, New York, New York 10065, USA
41. German Cancer Research Center, Division of Cancer Epidemiology, Postfach 101949, 69009 Heidelberg, Germany

**Corresponding author:**

Allan Jensen, Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100 Copenhagen O, Denmark

Phone: +45 35 25 76 93, Fax: +45 35 25 77 31, E-mail: [allan@cancer.dk](mailto:allan@cancer.dk)

**Abbreviations:** 95% CI: 95% confidence interval; BMI: Body mass index; OCAC: Ovarian Cancer Association Consortium; OR: odds ratio; pOR: pooled odds ratio; SES: socioeconomic status.

**Abstract**

**Purpose:** Socioeconomic status (SES) is a known predictor of survival for several cancers and it has been suggested that SES differences affecting tumour stage at diagnosis may be the most important explanatory factor for this. However, only a limited number of studies have investigated SES differences in tumour stage at diagnosis of ovarian cancer. In a pooled analysis, we investigated whether SES as represented by level of education is predictive for advanced tumour stage at diagnosis of ovarian cancer, overall and by histotype. The effect of cigarette smoking and body mass index (BMI) on the association was also evaluated.

**Methods**: From 18 case-control studies, we obtained information on 10,601 women diagnosed with epithelial ovarian cancer. Study specific odds ratios (ORs) with corresponding 95% confidence intervals (CI) were obtained from logistic regression models and combined into a pooled odds ratio (pOR) using a random effects model.

**Results:** Overall, women who completed ≤high school had an increased risk of advanced tumour stage at diagnosis compared with women who completed >high school (pOR 1.15; 95% CI 1.03-1.28). The risk estimates for the different histotypes of ovarian cancer resembled that observed for ovarian cancers combined but did not reach statistical significance. Our results were unchanged when we included BMI and cigarette smoking.

**Conclusion:** Lower level of education was associated with an increased risk of advanced tumour stage at diagnosis of ovarian cancer. The observed socioeconomic difference in stage at diagnosis of ovarian cancer calls for further studies on how to reduce this diagnostic delay.

**Keywords:** Epidemiology, ovarian cancer, pooled analysis, socioeconomic status, tumour stage

**1. Introduction**

Ovarian cancer is the 5th most common malignancy among women in developed countries [1]. Furthermore, it is a highly fatal disease with the worst prognosis among the gynaecological cancers because it is often diagnosed at an advanced tumour stage [2]. As tumour stage at diagnosis is among the most important prognostic factors in ovarian cancer, detection at an early stage is essential. However, currently there are no efficient screening tools for ovarian cancer and as most women only experience vague symptoms, the disease is often detected at an advanced stage when survival is poor. Therefore, knowledge on predictors for advanced stage at diagnosis of ovarian cancer is crucial to reduce the mortality for this disease.

Socioeconomic status (SES) is a predictor of incidence and survival of a number of diseases and there is evolving evidence for socioeconomic differences in cancer survival for many cancer types [3;4]. However, in contrast to breast cancer, relatively few studies have addressed the association between SES and ovarian cancer survival and the results have been inconsistent. Five studies [5-9] found worse survival among women with low SES whereas two studies [10;11] found no association. The reasons for socioeconomic differences in cancer survival in general and ovarian cancer survival in particular are not well-understood [4]. Possible underlying causes can be separated into three groups: tumour characteristics (tumour stage at diagnosis and biological characteristics), health care factors (e.g., types of treatment received, medical expertise and utilization of screening), and patient characteristics (e.g., lifestyle factors and comorbidities) [4]. According to Woods et al. [4], SES differences in tumour stage at diagnosis is likely the most important explanation for differences in cancer survival for a number of cancer types; including breast- [12], endometrial- [13] and cervical cancer [14]. SES differences in tumour stage at diagnosis may be attributable to several reasons, including access to and acceptance of cancer screening technologies, awareness of cancer symptoms, health-seeking behaviour, access to health care, comorbidities, and lifestyle factors.

However, only a limited number of studies have investigated SES differences in tumour stage at diagnosis of ovarian cancer, and whereas the majority found no convincing evidence that tumour stage at diagnosis differed according to SES [15-18], one recent study showed that a lower level of education was associated with advanced tumour stage at diagnosis of ovarian cancer [8]. Many of the previous studies were limited by small sample sizes and lack of individual level SES data, and none of the studies investigated whether the association between SES and tumour stage at diagnosis differed by histotype.

Using data from 18 case-control studies included in the international Ovarian Cancer Association Consortium (OCAC), we performed a pooled analysis in order to evaluate the association between SES (represented by highest obtained level of education) and tumour stage at diagnosis, overall and by histotype. Furthermore, we aimed to investigate to what degree the association between SES and tumour stage at diagnosis was confounded by pre-diagnosis cigarette smoking or by body mass index (BMI).

**2. Materials and Methods**

The Ovarian Cancer Association Consortium (OCAC) described in details elsewhere [19] is an international collaboration of case-control studies founded in 2005 with the original aim to identify genetic polymorphisms associated with ovarian carcinogenesis. More recently, consortial activities have included the identification of risk factors and prognostic factors for ovarian cancer. In the present study, we obtained data from 18 studies that provided information about level of education and other required variables for the study [20-37] (Table 1). All data were checked for internal consistencies and clarifications were provided by the original investigators if needed. Among women diagnosed with ovarian cancer, we excluded from analyses those with missing data for level of education, those with non-epithelial ovarian tumours or epithelial tumours of low malignant potential (borderline ovarian tumours) and those who lacked information on age, race/ethnicity or tumour stage at diagnosis, leaving 10,601 women for analysis. All individual studies included in OCAC had institutional review board or ethics committee approvals and all study participants provided informed consent.

**2.1. Assessment of level of education**

Information on highest attained level of education was obtained either from self-administered questionnaires (n = 8 studies) or from in-person interviews (n = 10 studies). For all included OCAC studies, information on highest level of education was harmonized and parameterized as a dichotomous variable (≤high school versus >high school).

**2.2. Statistical analysis**

Of the 18 studies included for analyses, 11 (AUS, GER, HOP, MAL, MAY, NCO, NEC, NTH, POL, SEA and UKO) used the FIGO staging system [38], while two studies (CON and NJO) used SEER staging manuals [39] to stage ovarian cancer. Five studies (DOV, HAW, STA, UCI and USC) had information on both FIGO and SEER tumour staging**.** In the common OCAC dataset, a harmonized summary tumour stage variable was created and reported in **the following categories: localized tumour stage, regional tumour stage or distant tumour stage, using the following algorithm: localized = FIGO tumour stage IA, IB, I (not other specified (NOS)) or SEER tumour stage 1; regional = FIGO tumour stage IC, IIA, IIB, IIC, II (NOS) or SEER tumour stage 2, 3, 4, 5; distant = FIGO tumour stage IIIA, IIIB, IIIC, III (NOS), IV or SEER tumour stage 7. For studies with information on both FIGO and SEER tumour staging, the harmonized summary tumour stage variable represents the more advanced of FIGO and SEER tumour stage. In all analyses, the harmonized OCAC tumour stage variable was parameterized as a dichotomous comparison of localized tumour stage or advanced tumour stage (regional or distant).**

To compare characteristics of the included women according to tumor stage at diagnosis (localized stage versus advanced stage), a Pearson's chi square statistical test was used when data were normally distributed (histology, level of education, smoking status and race/ethnicity) and a Wilcoxon rank sum statistical test was used when data were not normally distributed (age at diagnosis and BMI). We used a two-stage approach [40] to analyse the association between stage of ovarian cancer and level of education. First, study-specific odds ratios (ORs) were obtained by logistic regression models with adjustments for *a priori* selected potential confounding variables (described below). The study-specific estimates were then combined by random-effects inverse variance-weighted meta-analysis into a pooled odds ratio (pOR) with corresponding 95% confidence intervals (CIs) [41]. Statistical heterogeneity among studies was evaluated using the Cochran Q and I2 statistics. For all analyses, individual studies were included in the meta-analysis only if the following two requirements were met; i) five cases with complete data were available and ii) each level of the tumour stage variable had one or more subjects.

Two statistical models were fitted to evaluate the association of tumour stage at diagnosis of ovarian cancer according to level of education. Model 1 included adjustments for age at diagnosis (continuous variable) and race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian or other, including unknown races). In Model 2, we additionally adjusted for pre-diagnosis cigarette smoking (never, former or current smoker) and BMI (determined either at one or five years prior to ovarian cancer diagnosis, depending on the study) as a continuous variable (per 5 kg/m2). Subgroup analyses were conducted for specific histotypes of ovarian cancers including serous, mucinous, endometrioid and clear cell tumours. Serous tumours were additionally categorized as low- (grade 1) or high- (grade 2+) grade tumours. Finally, we also performed additional sensitivity analyses to investigate whether the association between level of education and tumour stage at diagnosis of ovarian cancer overall differed according to study continent (US versus non-US studies), race/ethnicity (white (non-Hispanic or Hispanic White) versus all other races/ethnicities (Black, Asian and other)) or study type (population-based versus hospital-/clinic-based studies). All analyses were conducted using the environment R, version 3.1.0. A 5% significance level was used for all analysis.

**3. Results**

Characteristics of the 18 studies that contributed data from 10,601 women with epithelial ovarian cancer are shown in Table 1. Eleven studies were conducted in the United States (US), six in Europe and one in Australia. In the studies, the number of women with ovarian cancer ranged from 183 to 1377. Women were 19-91 years of age at diagnosis between 1989 and 2010. Fifteen studies were population-based and three were hospital/clinic-based. Almost four-fifths of the women (78.6%) had advanced tumour stage (regional or distant) at diagnosis of ovarian cancer.

Table 2 presents characteristics of the women included in the analysis according to tumour stage at diagnosis of ovarian cancer. Among women diagnosed at advanced tumour stage, median age at diagnosis was significantly higher (58.0 years) compared with women diagnosed at localized tumour stage (median age = 53.0 years). Furthermore, women diagnosed at advanced tumour stage of ovarian cancer were more often diagnosed with serous tumours, had completed ≤high school, had higher BMI, were less likely to be Asian and were more often a former smoker, compared with women diagnosed at a localized tumour stage (all p-values < 0.01).

In Table 3 are presented the pooled odds ratios for advanced tumour stage at diagnosis of ovarian cancer overall and within histotypes according to level of education. The table shows pORs based on two analytic models: Model 1 includes adjustment for age and race/ethnicity and Model 2 includes additional adjustment for BMI and cigarette smoking status. Women who completed high school or less had an increased risk of advanced tumour stage at diagnosis of ovarian cancer (pOR 1.15; 95% CI 1.03-1.28) (Table 3, Model 1; Figure 1). The risk estimates for the various histotypes generally resembled that for ovarian cancer overall, though none of the risk estimates reached nominal statistical significance (Table 3, Model 1). Additional adjustments for BMI and cigarette smoking status made virtually no changes to the estimated associations between level of education and tumour stage at diagnosis of ovarian cancer (Table 3, Model 2). Heterogeneity was not evident for any of the analyses included in the present paper (All p-values > 0.4 and all I2 <5%).

Lastly, we performed sensitivity analyses to investigate whether the association between level of education and tumour stage at diagnosis of ovarian cancer overall differed according to study continent, race/ethnicity or study type. However, the direction and the magnitude of the associations were not markedly different from the associations obtained in the main analyses (Table 3). Further, the risk estimates did not differ statistically significantly between the US studies (pOR 1.11; 95% CI 0.97-1.28) and the non-US studies (pOR 1.22; 95% CI 1.01-1.47), between women of white race/ethnicity (pOR 1.15; 95% CI 1.02-1.29) and women of other races/ethnicities (pOR 1.13; 95% CI 0.84-1.51), as well as between population-based studies (pOR 1.14; 95% CI 1.01-1.28) and hospital-/clinic-based studies (pOR 1.28; 95% CI 0.88-1.73) (all p-values for pairwise comparisons >0.05).

**4. Discussion**

Tumour stage is the most important prognostic factor of survival in ovarian cancer. It is therefore important to identify factors that predict tumour stage at diagnosis. A potential candidate is socioeconomic status, which has been found to be associated with tumour stage at diagnosis for other gynaecological cancers [12-14]. The present large study evaluated the association between level of education and tumour stage at diagnosis of epithelial ovarian cancer. Our results showed that women who completed high school or less had a modest (15%) increased risk of advanced tumour stage at diagnosis of ovarian cancer compared with women who completed more than high school. Observed risk estimates for the histotypes resembled those for ovarian cancer overall.

Only a few studies have investigated SES differences in tumour stage at diagnosis of ovarian cancer. Our results are partly in line with results from a recent Danish cohort study. Ibfelt et al. [8], with data of 2873 women diagnosed with ovarian cancer, observed that women with medium level of education (10-12 years) had a 25% increased risk of advanced tumour stage at diagnosis of ovarian cancer compared with women with high level of education (>12 years). However, the authors found no association between risk of advanced tumour stage and short level of education (7-9 years). Other studies have found no convincing associations between various measures of SES and tumour stage at diagnosis of ovarian cancer [15-18]. For example, in the largest study to date using data from 16,228 American women with ovarian cancer, Morris et al. [18] found no association between a census-based measure of SES and tumour stage at diagnosis. An explanation for the divergent results may be that only our study and the study by Ibfelt et al. [8] used individual level measures of SES, whereas all other studies of this question have used various area-based/aggregate measures of SES as surrogates for individual SES. Area-based and aggregate measures of SES are known to be less precise (i.e., have higher risk of misclassification) than individual measures of SES and likely to bias relative risk toward the null in epidemiological studies [42]. No previous studies have examined whether or not the association between SES and tumour stage at diagnosis of ovarian cancer differs by histotype. We observed that the estimated risks for the histotypes of ovarian cancer resembled that for ovarian cancer overall. However, the numbers of cases for some of the histotypes were relatively small and additional confirmation would be warranted.

The observed association between educational level and tumour stage at diagnosis is likely to be explained by a complex interaction between several underlying factors, including patient access to regular health-care check-ups, patient awareness of cancer symptoms, adequate reaction to symptoms, access, barriers and quality of healthcare, time-period to referral to specialist care, lifestyle factors, and comorbidities. Cancer symptom awareness and interpretation of symptoms is poorer among those who are less educated and those with lower SES [43]. Though some ovarian cancers are asymptomatic, most women experience vague or non-specific symptoms, which are similar to those of other common illnesses [44]. Therefore, it is plausible that more highly educated women could be more aware of and able to recognize potential symptoms compared with less educated women and may therefore be more likely to seek medical care earlier, which would eventually lead to a diagnosis of ovarian cancer in an earlier tumour stage. However, compared with cancers that are generally screenable or present with clear clinical signs, the potential for socioeconomic status to have an influence on awareness of symptoms and health-care seeking in ovarian cancer are likely to be rather limited. Alternatively, women that are more educated might respond more promptly to their apparent signs or symptoms whereas less educated women may be more likely to ignore, discount or deny them until mounting discomfort becomes substantial in advanced tumour stage disease.

Regular visits to a primary care physician and the latency from date of visit at the general practitioner until referral to a gynaecologist are both factors that are potentially predictive for tumour stage at diagnosis of ovarian cancer. As low SES is associated with less frequent use of primary care [45] and likely increased time to referral to a specialist, these factors may combine to explain the observed association between educational level and tumour stage at diagnosis. In the present study, 11 of 18 individual studies were conducted in the USA, representing 65% of the women in our study population. In contrast to Europe and Australia, access to health care in the USA is not uniform and a larger proportion of well-educated American women are privately insured compared with less educated American women. It is plausible that women with private health insurance visit a primary care physician more regularly and are faster referred to a gynaecologist compared with women who are uninsured or covered by governmental insurance programs. Therefore, it would be reasonable to assume that the association between level of education and tumour stage at diagnosis of ovarian cancer would be more pronounced among the US studies than among the non-US studies. However, the results from our additional analysis stratified by study continent were not able to support this.

Finally, low SES is known to be associated with less unhealthy lifestyle, including factors such as poorer diet, less exercise, more cigarette smoking and higher BMI [46-48]. Both cigarette smoking and obesity accelerates carcinogenesis resulting in earlier progression and death, whereas obesity can blur ovarian cancer symptoms and delay diagnosis [49]. However, in the present study, BMI and cigarette smoking status had virtually no effect on the estimated associations between level of education and tumour stage at diagnosis. Therefore, BMI and cigarette smoking do not appear to have substantial influence on tumour stage difference by level of education.

A strength of the present study is the large number of ovarian cancer patients obtained by pooling data from 18 individual case-control studies. This collection strengthened the statistical power of the risk estimates and allowed us to examine associations both overall and separately for the various histotypes of ovarian cancer. In addition, the majority of the studies were population-based designs with information on education obtained from in-person interviews. The participating studies were not selected from among published studies. Therefore, our analyses included both positive and negative study-specific results, limiting the possibility of publication bias. The present analyses relied on individual data combined into a single dataset following careful central data harmonization. We considered differences in study design and data collection across studies and adjusted for relevant confounding factors across studies. However, we could not adjust for comorbidity, as this information was not available in our data. The degree of comorbidity is known to be inversely correlated with SES [50] and comorbidity may blur symptoms of cancer and may reduce individual resources when it comes to health care seeking. Hence, even though a recent cohort study showed that comorbidity only had a small impact on the differences in ovarian cancer stage and survival by SES [8], we cannot rule out that our results may have been slightly affected by unmeasured confounding from comorbidity. Furthermore, information on tumour stage was abstracted from hospital records or cancer registries and the majority of study sites performed pathology review in order to confirm histotype classifications. Nevertheless, not all ovarian tumours underwent systematic histopathologic review and therefore some degree of misclassification of subtype could have occurred. An additional potential limitation of the present study is that we only included one measure of SES - level of education - as only a limited number of OCAC studies obtained information on other measures such as income or marriage/cohabitation status. Even though a single measure of SES may show an association with the health outcome analysed, it may not encompass the entirety of the effect of SES on health, and inclusion of multiple measures of SES are always preferable [51]. Hence, by including only one measure of SES, we may only partly have explained the true association between SES and stage at diagnosis of ovarian cancer. However, level of education is considered to be a good and valid measure of SES with regard to health because it influences an individuals’ SES throughout life and it is highly associated with both income and occupation [6; 52]. Further, knowledge and skills obtained through education may affect cognitive functions and thereby strengthen the individuals’ comprehension of health messages and communication with health authorities [51]. Finally and perhaps most importantly, for most individuals, level of education does not change substantially throughout life compared with other measures of SES, including income and occupation, and can therefore be considered to be a robust measure of SES [51].

**5. Conclusions**

This large pooled analysis showed that lower educational level was associated with advanced tumour stage at diagnosis. BMI and cigarette smoking did not explain the association. Hence, in order to reduce diagnostic delays, it is important to identify which underlying factors (e.g., patient awareness of and response to cancer symptoms, access to healthcare and latency of referral to specialist care, lifestyle factors and comorbidities) that contribute to socioeconomic differences in tumour stage at diagnosis of ovarian cancer.

**Conflicts of interest: None**

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**Table 1** Characteristics of the 18 case-control studies included in the pooled analysis of level of education and stage at diagnosis of ovarian cancer.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Region** | **Study** | **Study acronym** |  | **Study period** |  | **Cases**  **N** |  | **Women diagnosed at advanced**  **tumour stagea**  **(%)** |  | **Study type** |  | **Age range** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Australia | Australian Ovarian Cancer Study and | AUS |  | 2002-2006 |  | 1,073 |  | 950 (88.5) |  | Population-based |  | 20-80 |
|  | Australian Cancer Study (Ovarian Cancer) |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Europe | German Ovarian Cancer Study | GER |  | 1993-1996 |  | 219 |  | 178 (81.3) |  | Population-based |  | 21-75 |
|  |  |  |  |  |  |  |  |  |  |  |  | 32-80 |
|  | The Danish Malignant Ovarian Tumor Study | MAL |  | 1994-1999 |  | 551 |  | 478 (86.8) |  | Population-based |  | 32-80 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Nijmegen Ovarian Cancer Study | NTH |  | 1989-2006 |  | 254 |  | 172 (67.7) |  | Hospital-based |  | 23-83 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Polish Ovarian Cancer Case-Control Study | POL |  | 2000-2003 |  | 183 |  | 112 (61.2) |  | Population-based |  | 27-74 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Study of Epidemiology and Risk Factors in | SEA |  | 1998-2010 |  | 917 |  | 522 (56.9) |  | Population-based |  | 22-74 |
|  | Cancer Heredity |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | UK Ovarian Cancer Population Study | UKO |  | 2006-2010 |  | 524 |  | 443 (84.5) |  | Hospital-based |  | 19-89 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| United States (US) | Connecticut Ovarian Cancer Study | CON |  | 1998-2003 |  | 296 |  | 248 (83.8) |  | Population-based |  | 36-81 |
|  | Diseases of the Ovary and their evaluation | DOV |  | 2002-2005 |  | 592 |  | 504 (85.1) |  | Population-based |  | 35-74 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Hawaii Ovarian Cancer Case-Control Study | HAW |  | 1993-2008 |  | 681 |  | 486 (71.4) |  | Population-based |  | 24-87 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Novel Risk Factors and Potential Early Detection | HOP |  | 2003-2009 |  | 663 |  | 552 (83.3) |  | Population-based |  | 25-91 |
|  | Markers for Ovarian Cancer |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Mayo Clinic Ovarian Cancer Case-Control | MAY |  | 2000-2009 |  | 493 |  | 450 (91.3) |  | Clinic-based |  | 21-91 |
|  | Control Study |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | North Carolina Ovarian Cancer study | NCO |  | 1999-2008 |  | 849 |  | 723 (85.2) |  | Population-based |  | 22-74 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | New England Case-Control Study | NEC |  | 1992-2003 |  | 827 |  | 570 (68.9) |  | Population-based |  | 21-77 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | New Jersey Ovarian Cancer Study | NJO |  | 2002-2008 |  | 230 |  | 184 (80.0) |  | Population-based |  | 30-81 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Family Registry for Ovarian Cancer and | STA |  | 1997-2001 |  | 488 |  | 376 (77.0) |  | Population-based |  | 21-64 |
|  | Genetic Epidemiology of Ovarian Cancer |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | University California Irvine Ovarian Study | UCI |  | 1993-2005 |  | 384 |  | 310 (80.7) |  | Population-based |  | 21-86 |
|  | Los Angeles County Case-Control Studies of | USC |  | 1993-2005 |  | 1,377 |  | 1,073 (77.9) |  | Population-based |  | 20-84 |
|  | Ovarian Cancer |  |  |  |  |  |  |  |  |  |  |  |
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|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **TOTAL** |  |  |  |  |  | **10,601** |  | **8,331 (78,6)** |  |  |  | **19-91** |

a Women diagnosed with regional or distant stage

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2** Characteristics of women diagnosed with epithelial ovarian cancer, according to tumour stage at  diagnosis. | | | | | | | | |
|  |  | **All** |  | **Localized stage** |  | **Advanced stageb** |  |  |
|  |  | **(n = 10,601)** |  | **(n = 2,270)** |  | **(n = 8,331)** |  | **P-value** |
|  |  |  |  |  |  |  |  |  |
| **Age at diagnosis (years)** |  |  |  |  |  |  |  |  |
| Median |  | 57.0 |  | 53.0 |  | 58.0 |  | <0.001c |
| Interquartile range |  | 49.0-65.0 |  | 45.7-62.0 |  | 50.0-66.0 |  |  |
| **Histology** |  |  |  |  |  |  |  |  |
| Serous |  | 6,066 (57.2) |  | 501 (22.1) |  | 5,565 (66.8) |  | <0.001d |
| Serous low-grade |  | 479 (4.5) |  | 98 (4.3) |  | 381 (4.6) |  |  |
| Serous high-grade |  | 5,030 (47.4) |  | 339 (14.9) |  | 4,691 (56.3) |  |  |
| Endometrioid |  | 1,664 (15.7) |  | 665 (29.3) |  | 999 (12.0) |  |  |
| Mucinous |  | 780 (7.4) |  | 480 (21.1) |  | 300 (3.6) |  |  |
| Clear cell |  | 875 (8.3) |  | 412 (18.1) |  | 463 (5.6) |  |  |
| Othera |  | 1,216 (11.5) |  | 212 (9.3) |  | 1,004 (12.1) |  |  |
|  |  |  |  |  |  |  |  |  |
| **Level of education** |  |  |  |  |  |  |  |  |
| ≤High school |  | 5,190 (49.0) |  | 1,054 (46.4) |  | 4,136 (49.6) |  | 0.008d |
| >High school |  | 5,411 (51.0) |  | 1,216 (53.6) |  | 4,195 (50.4) |  |  |
|  |  |  |  |  |  |  |  |  |
| **BMI** |  |  |  |  |  |  |  |  |
| Median |  | 24.0 |  | 23.6 |  | 24.1 |  | <0.001c |
| Interquartile range |  | 21.4-28.2 |  | 20.9-28.0 |  | 21.5-28.2 |  |  |
| **Smoking status** |  |  |  |  |  |  |  | 0.02d |
| Never |  | 5,770 (54.4) |  | 1,227 (54.1) |  | 4,543 (54.5) |  |  |
| Former |  | 3,391 (32.0) |  | 694 (30.6) |  | 2,697 (32.4) |  |  |
| Current |  | 1,440 (13.6) |  | 349 (15.4) |  | 1,091 (13.1) |  |  |
|  |  |  |  |  |  |  |  |  |
| **Race/ethnicity** |  |  |  |  |  |  |  | <0.001d |
| Non-Hispanic White |  | 9,129 (86.1) |  | 1,878 (82.7) |  | 7,251 (87.0) |  |  |
| Hispanic White |  | 306 (2.9) |  | 62 (2.7) |  | 244 (2.9) |  |  |
| Black |  | 265 (2.5) |  | 53 (2.3) |  | 212 (2.5) |  |  |
| Asian |  | 565 (5.3) |  | 190 (8.4) |  | 375 (4.5) |  |  |
| Other |  | 331 (3.1) |  | 87 (3.8) |  | 244 (2.9) |  |  |

a Includes mixed cell, undifferentiated and tumours of unknown histology

b Includes regional or distant stage

c The P-value was calculated using the Wilcoxon rank sum statistical test as the data were not normally distributed

d The P-value was calculated using the Pearson’s chi square statistical test at the data were normally distributed

Numbers may not sum up to total because of missing data

**Table 3** Adjusted pooled odds ratios (pORs) and 95% confidence intervals (95% CI) for the association

between level of education and advanced stage at diagnosis of ovarian cancer, overall and by histotype.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Model 1a** | | |  | **Model 2b** | | |
|  |  | **Cases (n = 10,601)** |  | **pOR (95% CI)** |  | **Cases (n = 10,457)** |  | **pOR (95% CI)** |
| **Overall** |  |  |  |  |  |  |  |  |
| >high school |  | 5,411 |  | 1.00 |  | 5,362 |  | 1.00 |
| ≤high school |  | 5,190 |  | 1.15 (1.03-1.28) |  | 5,095 |  | 1.18 (1.05-1.32) |
|  |  |  |  |  |  |  |  |  |
| **Serous** |  |  |  |  |  |  |  |  |
| >high school |  | 3,003 |  | 1.00 |  | 2,973 |  | 1.00 |
| ≤high school |  | 3,063 |  | 1.08 (0.87-1.34) |  | 3,009 |  | 1.13 (0.90-1.41) |
|  |  |  |  |  |  |  |  |  |
| **Serous low-grade** |  |  |  |  |  |  |  |  |
| >high school |  | 143 |  | 1.00 |  | 142 |  | 1.00 |
| ≤high school |  | 228 |  | 1.10 (0.51-2.35) |  | 228 |  | 1.23 (0.49-3.12) |
|  |  |  |  |  |  |  |  |  |
| **Serous high-grade** |  |  |  |  |  |  |  |  |
| >high school |  | 2,568 |  | 1.00 |  | 2,541 |  | 1.00 |
| ≤high school |  | 2,462 |  | 1.02 (0.78-1.32) |  | 2,413 |  | 1.09 (0.83-1.43) |
|  |  |  |  |  |  |  |  |  |
| **Endometrioid** |  |  |  |  |  |  |  |  |
| >high school |  | 908 |  | 1.00 |  | 901 |  | 1.00 |
| ≤high school |  | 756 |  | 1.10 (0.86-1.42) |  | 749 |  | 1.17 (0.90-1.53) |
|  |  |  |  |  |  |  |  |  |
| **Mucinous** |  |  |  |  |  |  |  |  |
| >high school |  | 349 |  | 1.00 |  | 349 |  | 1.00 |
| ≤high school |  | 271 |  | 0.97 (0.63-1.48) |  | 266 |  | 1.09 (0.68-1.76) |
|  |  |  |  |  |  |  |  |  |
| **Clear cell** |  |  |  |  |  |  |  |  |
| >high school |  | 436 |  | 1.00 |  | 431 |  | 1.00 |
| ≤high school |  | 390 |  | 1.19 (0.84-1.71) |  | 376 |  | 1.21 (0.83-1.77) |

aAdjusted for age (continuous variable) and race/ethnicity (Non-Hispanic White, Hispanic White, Black, Asian and other).

bAdjusted for the two factors in Model 1 plus adjustment for BMI (continuous variable) and cigarette smoking status (never, former or current).

**Figure Legends**

**Fig. 1.** Risk of advanced tumour stage at diagnosis of ovarian cancer associated with level of education by study site and overall. Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression models adjusted for age and race/ethnicity. The pooled odds ratio (pOR) with corresponding 95% CI was estimated using a random effects model. Level of education was parameterized as women who completed high school or less versus women who completed more than high school

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