National population-based case-control study regarding Pelvic Inflammatory Disease and subsequent risk of Epithelial Ovarian Cancer

-SPICA-

Research plan

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Background

Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian cancers. It was once thought of as one single disease however based on histopathology, immunohistochemistry and genetic analyzes five main subtypes are identified; high-grade serous (HGSC) (70%), low-grade serous (LGSC) (<5%), endometrioid (10%), clear cell (10%) and mucinous (3%) (1). The exact pathogenesis of EOC is still not fully understood. Many risk factors for EOC are related to repeated ovulation, and inflammation has been hypothesized as a potential mechanism of ovarian carcinogenesis (2-4). Microorganisms causing chronic inflammation have become increasingly investigated in the last decade as possible cancer initiators/promoters in many different types of cancers. In experimental animal models, the sexually transmitted bacteria *Chlamydia trachomatis* (*C. trachomatis*) has been shown to infect the same cells in the fallopian tube where HGSC originate (5, 6). Furthermore, the bacterium has been found in fallopian tube and ovarian tumor tissues (7-9) both suggesting that the bacterium may impact ovarian tumorigenesis. Three recent large seroepidemiological studies have shown association between *C. trachomatis* antibodies and increased risk of EOC (10-12). *C. trachomatis* infection causes cervicitis and if not resolved ascends to the upper genital tract causing pelvic inflammatory disease (PID). PID is described as inflammation of the female reproductive organs as a result of ascending microorganisms from the lower genital tract and includes endometritis, salpingitis, oophoritis, pelvic peritonitis and tubo-ovarian abscess (13). The exact incidence of PID is unknown, there is probably an underestimation of the incidence since many women do not seek medical care due to no or mild unspecific symptoms. Treatment of PID has also varied over time, in 1960's all women diagnosed with PID were hospitalized and prescribed bed rest, however nowadays many women are diagnosed and treated in outpatient settings by their gynecologist or by their general practitioners. The clinical and microbiological cure rate of PID after antibiotics have been reported to be high however the risk of sequels depends on the severity of infection before treatment. Nulliparity and infertility are both consequences of PID and associated with increased risk for EOC (14). On the contrary tubal ligation and hysterectomy have been associated with reduced risk of ovarian cancer (15, 16), potentially because it prevents infectious agents to ascend to the upper genital tract and cause inflammation. The association of PID with EOC has been investigated by a number of authors with contradictory findings, some find increased risk of EOC associated with PID (3, 17-21), whereas others do not find associations (22-24).

In summary, the results regarding the risk of EOC after a diagnosis of PID are inconsistent and most studies are limited by case-control design with retrospective recall and various time of follow-up (1-35 years depending on the studies). There is a limited number of large, population-based studies with well-defined participants and hospital-based diagnosis to verify the association further.

Aim

The overall aim is to study if clinical PID is associated with subsequent increased risk of EOC, and if a history of PID affects the prognosis of EOC.

Specific aims

The specific aims are to answer the following questions:

- Is PID associated with EOC?
- Is PID differentially associated with the different EOC histotypes?
- Is PID differentially associated with tumors of different locations (ovaries, fallopian tube, abdominis or pelvis)?
- Is PID associated with tumor spread (FIGO stage)?
- Is PID associated with prognosis after an EOC diagnosis?

Material & Methods

Cohort

This nation-wide population-based case-control study will consist of all women residing in Sweden and diagnosed with EOC between 1999 up until 2020. Around 630 women are diagnosed with EOC each year in Sweden, consequently we expect to include approximately 13 000 women with EOC. Cases will be identified through the Swedish Cancer Register (SCR), which was established in 1958 and contains data on histologically verified cancers. Coverage is secured by mandatory duty for health care providers to register all patients with malignant conditions. A Swedish study estimated that the overall completeness of SCR year 1998 to be more than 95% (25). From year 1993 and onwards the site of tumors was coded according to the International Classification of Diseases, Revision 10 (ICD-10). Tumor spread has been registered since 2004. The National Quality Register of Gynecologic cancer started in 2008 and contains information regarding histopathology and tumor spread. Cases will be matched to ten controls each, with respect to year of birth and parish at time of diagnosis of the index case.

We will identify women in the case-control cohort that have a PID diagnosis prior to the EOC diagnosis for the index-case through the Swedish Patient Register. In Sweden, about 1300 women/year are diagnosed with salpingitis/oophoritis and 2000 women/year are diagnosed with endometritis. The Patient Register was established in 1964 and reached nationwide coverage 1987. The register contains individual data on hospital admission, major interventions, discharge and discharge diagnosis. From 2001 the register was supplemented with specialized outpatient care. The diagnoses are coded according to the ICD-10 from 1964 and onwards (earlier ICD codes have been translated into ICD-10). The surgical interventions are coded according to the Swedish Classification of Operations and Major Procedures.

Primary outcome

EOC, cases will be selected by ICD-10 codes.

Secondary outcomes

1. EOC histotypes, eg. high-grade serous, low-grade serous, clear cell, mucinous and endometrioid cancer.
2. Tumor locations, eg. ovaries, salpinx, serous surface papillary carcinoma (SSPC), abdominis and pelvis.
3. Tumor spread (FIGO stage).
4. Progression free (PFS) and overall survival (OS).

Exposure

PID, i.e. inflammation of the female reproductive organs including; salpingitis, oophoritis and endometritis.

Exclusion criteria

Controls will be excluded if they have had bilateral oophorectomy before the date of cancer diagnosis of the index case. Furthermore, included women must have been residing in Sweden since the age of 18 so that participants with potential PID are included in Swedish Health registers.

Potential confounders

Parity, known to impact ovarian cancer risk, will be collected from the Multi-Generation Registry containing full coverage from women giving birth from 1920 and onwards.

Gynecologic surgery data (salpingectomy/hysterectomy/unilateral salpingo-oophoroectomy/tubal ligation) as well as infertility and endometriosis will be collected from the Patient Registry and supplemented with data from the Swedish National Quality Registry of Gynecological Surgery (GynOp), established 1997, to extend the completeness.

Educational level and income, as a proxy for socioeconomic level, will be extracted from the Longitudinal Integration database for health insurance and labor market studies (LISA). LISA started in 1990 and contains data on highest level of education from all persons 16 years of age and older who have been registered in Sweden.

Drug therapies may modify the risk of ovarian cancer. Menopausal hormone therapy (MHT) to treat symptoms associated with female menopause may increase ovarian cancer risk if used for more than five years (14). Combined oral contraceptives (COC) is on the other hand well known to reduce ovarian cancer risk (14). Daily use of anti-inflammatory tablets like low-dose aspirin has also been associated with reduced risk of EOC (26-28). Data regarding COC, MHT and anti-inflammatory treatment will be extracted from the Swedish Drug Register, established in 2005, contains data on all prescription medicines collected at Swedish pharmacies. However, since women are often younger when taking oral contraceptives and the register started in 2005, this factor can only be adjusted for in a smaller subgroup of younger women. In vitro studies have shown that chlamydiae bacteria can either be eradicated but also potentially develop into a more persistent state after exposure to antibiotic treatment (29). Therefore, chlamydia specific antibiotics will be extracted from the Swedish Drug Register.

Survival data

In the case-cohort we will investigate if PID is associated with specific tumor locations, tumor spread and/or death among women with EOC. Tumor spread can be identified using the Swedish National Quality Registry of Gynecological Surgery from late nineties in addition to the SCR from year 2004. Information on year of death and cause of death will be collected from the SCR that have withdrawn that information from the Swedish Cause of Death Registry. To reduce any loss of survival data from cases after receiving an EOC diagnosis, information on migration will be retrieved from the Swedish Population Register.

Ethical considerations

The individuals included in the study will not be exposed to any harm. Data will be delivered to the researcher coded and the results will be analyzed at group level. In a wider perspective, the project can provide an increased understanding of the causal mechanisms behind ovarian cancer development. If we can verify an association between PID and ovarian cancer it would emphasize both for women and to clinicians the importance of prevention, discovery, diagnosis and treatment of PID.

Data protection

The data will be pseudo-anonymized and given a code. The code key will be kept at National Board of Health and Welfare and initially stored for three years. If an application for extended storage is submitted and approved the data may be stored for longer. The coded work material is stored in Sarah Jonsson personal work computer with backup system at Umeå University. Original data will be stored in a central data-base at Umeå University for at least 10 years.

Statistical methods

Pseudonymized data will be analyzed and suitable analysis will be performed including conditional logistic regression. Stratification based on histotypes, tumor locations, tumor spread, age-groups and lag-time will be performed, and tests for heterogeneity carried out. Results will be adjusted for various

potential confounders, that will be predefined by directed acyclic graphs, in multivariable regression analyses and modeling. Survival analyses. Several sensitivity analyses will be performed.

Impact

This is the first population-based study in Sweden investigating the association between clinical PID and subsequent risk for EOC with adequate follow-up time. If this study can verify an association, it could increase the populations and clinician's awareness of the fatal consequences of PID. It could generate a more vigilant approach to screening, diagnostics as well as treatment primarily against PID including *C. trachomatis* which is the most common bacterial cause of PID. All in all, in the long term, it would potentially reduce ovarian cancer incidence.

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Variabler

Fallen

Kvinnor boende i Sverige från 18 års ålder och med diagnosen EOC (se lista nedan) mellan 1999-2020:
C48.1-2 Malign tumör i bukhinnan spec/ospec lokalisation
och / eller
C56.9 Malign tumör i äggstock
och / eller
C57.0-9 Malign tumör i andra och ospecificerade kvinnliga könsorgan inkl äggledare
och / eller
C76.2-3 Malign tumör i buken eller Malign tumör i bäckenet
och / eller
D39.1 Borderline tumör i äggstock

Kontroller

Kvinnor utan ovanstående EOC diagnos innan index-fallets diagnosdatum.
Boende i Sverige från 18 års ålder. Matchas 10:1.

Exklusion

Bilateral ooforektomi eller bilateral salpingooforektomi *före* indexfallets diagnosdatum.
Även två gånger unilateral ooforektomi eller unilateral salpingooforektomi *före* indexfallets diagnosdatum är uteslutningskriterium.
Åtgärds koder: LAE20, LAE21, LAF10, LAF11, LAF30, 7021, 7022, 7031, 7032

Exponering ”Bäckeninflammation/PID”

N70.0-9 Salpingit och ooforit (inflammation i äggledare och äggstock)
N71.0-9 Inflammatorisk sjukdom i livmodern utom livmoderhalsen
N73.0-9 Andra inflammatoriska sjukdomar i det kvinnliga bäckenet
N74.0-9 Inflammatoriska tillstånd i det kvinnliga bäckenet vid sjukdomar som klassificeras annorstädes
N76.8-W Annan specificerad inflammation i vagina och vulva *Bakteriell vaginos*
B37.3 Candidainfektion i vulva/vagina
A56.0-8 Klamydiainfektion i nedre delen av urin- och könsorganen

Förväxlingsfaktorer

N80.0-9 *Endometrios*
N97.8 *Infertilitet*
O00.0-9 *Utomkvedshavandeskap*

Läkemedel
G03AA/G03AB/G03AC Hormonella antikonceptionella medel för systemisk bruk
G03CA03, G03CX01 Östradiol & Tibolon
G03FA/G03FB Gestagener i kombination med östrogener & sekvenspreparat
M01AA/M01AB/ M01AC/M01AE; M01AG/M01AH/M01AX Icke-steroida antiinflammatoriska
N02BA/N02BE Övrig analgetika och antipyretika
B01AC04/B01AC06 Trombocytaggregationshämmande medel (med antiinflammatorisk verkan)
J01AA02 Tetracykliner / *Doxycyklin*

J01CA04 Penicilliner med utvidgat spektrum / *Amoxicillin*
J01FA01/J01FA10 Makrolider /*Erytromycin Azitromycin*
J01MA02 Antibakteriella kinolonderivat / *Ciprofloxacin*

Tidigare gynoperationer med följande åtgärdskoder:
LAE10-21, LAF00-30, LAW96-97 Operationer på äggstock
LBC00-98, LBD00-01, LBE00-03, LBF20-98, LBW96-98 Operationer på äggledare
LCC01, LCC10, LCD00-97, LCE00-96, LCH00-96 Operation på livmoder
LGA00-98 Steriliseringsoperation

Gammalt kodverk "Klassificering av operation 1963-1996" se bifogad K06 dokument*:*
7020, 7021, 7022, 7030, 7031, 7032,
7100, 7110, 7111, 7120, 7121
7140,7141, 7142, 7143, 7144, 7145, 7146, 7148
7150, 7151, 7152
7190, 7196, 7199,
7210, 7211, 7220, 7221, 7222, 7223, 7228
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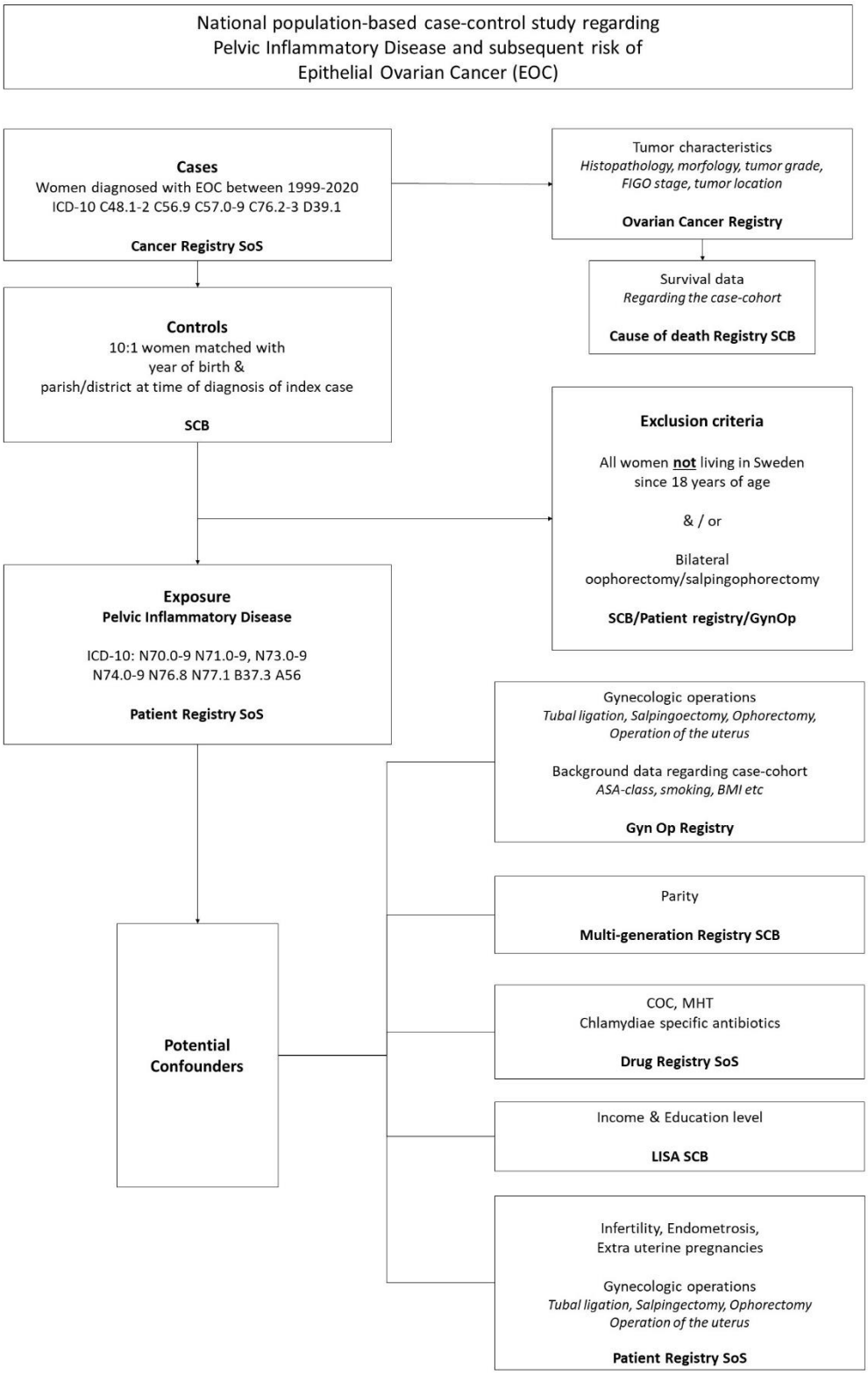
7260, 7261, 7262, 7263
7270, 7271, 7272, 7273, 7274, 7275, 7276, 7277, 7279
7467


National population-based case-control study regarding
Pelvic Inflammatory Disease and subsequent risk of
Epithelial Ovarian Cancer (EOC)
Cases
Women diagnosed with EOC between 1999-2020
ICD-10 C48.1-2 C56.9 C57.0-9 C76.2-3 D39.1
Cancer Registry SoS
Tumor characteristics
Histopathology, morfology, tumor grade,
FIGO stage, tumor location
Ovarian Cancer Registry
Survival data
Regarding the case-cohort
Cause of death Registry SCB
Controls
10:1 women matched with
year of birth &
parish/district at time of diagnosis of index case
SCB
Exclusion criteria
All women not living in Sweden
since 18 years of age
& / or
Bilateral
oophorectomy/salpingophorectomy
SCB/Patient registry/GynOp
Exposure
Pelvic Inflammatory Disease
ICD-10: N70.0-9 N71.0-9, N73.0-9
N74.0-9 N76.8 N77.1 B37.3 A56
Patient Registry SoS
Gynecologic operations
Tubal ligation, Salpingoectomy, Ophorectomy,
Operation of the uterus
Background data regarding case-cohort
ASA-class, smoking, BMI etc
Gyn Op Registry
Parity
Multi-generation Registry SCB
COC, MHT
Chlamydiae specific antibiotics
Drug Registry SoS
Income & Education level
LISA SCB
Infertility, Endometrosis,
Extra uterine pregnancies
Gynecologic operations
Tubal ligation, Salpingectomy, Ophorectomy
Operation of the uterus
Patient Registry SoS
Potential
Confounders