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Social support and ovarian cancer incidence – A Swedish prospective population-based study

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HIGHLIGHTS

- This study includes 58,000 women from a prospective Swedish cohort with 239 epithelial ovarian cancer cases.
- A validated version (SS13) of the Interview Schedule for Social Interaction (ISSI) was used.
- Quantitative (AVSI) and qualitative (AVAT) aspects of self-perceived social support were measured.
- Serous epithelial ovarian cancer was significantly associated with low scores of AVSI.
- Overall, neither AVSI nor AVAT were associated with the incidence of epithelial ovarian cancer.

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ABSTRACT

Objective. Low social support is associated with worse prognosis for epithelial ovarian cancer (EOC) patients. However, few studies have explored the relation between low social support and *incidence* of EOC. The aim of this prospective nested case-control study was to examine whether self-perceived low social support was associated with the incidence of EOC.

Methods. The Swedish Cancer Registry was used to identify participants in the Västerbotten Intervention Programme (VIP) comprising 58,000 women, who later developed EOC. Each case was matched to four cancer free controls. The VIP uses the Social Support questionnaire, a modified version of the validated questionnaire "The Interview Schedule for Social Interaction" (ISSI) measuring quantitative (AVSI) and qualitative (AVAT) aspects of social support.

Results. The risk of EOC in relation to AVSI and AVAT was similar between the 239 cases and the 941 controls after adjustment for educational level, smoking, BMI, Cambridge Physical Activity Index and age (aOR 0.85, 95% CI 0.72–1.01 and aOR 0.54, 95% CI 0.16–1.81). Lagtime was found to have no impact. A decreased risk of serous ovarian cancer was seen in women with fewer persons available for informal socializing (aOR 0.75, 95% CI 0.59–0.95). Adjusted analyses showed non-significant odds ratios below 1.0 in the vast majority of histotypes.

Conclusions. A general trend towards a decreased risk of ovarian cancer associated with low AVSI and AVAT was identified. Solely the serous subtype was significantly associated with low scores of AVSI. Prospective pathophysiological and epidemiological studies regarding social support are needed.

1. Introduction

Epithelial ovarian cancer (EOC) is the sixth most common cancer among women and has the highest mortality rate of all gynaecological cancers [1]. Even though life style factors such as overweight and smoking have shown some association with incidence of EOC, few modifiable major risk factors have been identified apart from those related to reproduction [2].

In a general population, low social support is associated with higher all-cause morbidity and mortality [3,4]. One considered reason for this association is the effect of social support on neuroendocrine regulation [5,6]. Persons with low social support show elevated levels of catecholamines in blood and urine [3–5]. Changes in activity pattern of the sympathetic nervous system, including catecholamine signalling, have been identified as one etiological factor in cancer pathogenesis [7]. Catecholamines activate β_2-adrenergic receptors and a downstream effect of this activation is an increase in radical oxygen species that causes DNA damage. Activation of β_2-adrenergic receptors also results in a downregulation of the tumor suppressor p53 [8,9]. In animal models, stress generates substantial growth of EOC cells, effectuated by norepinephrine

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and inhibited by beta-blockers [10,11]. Norepinephrine also amplifies the expression of interleukin 8 (IL-8) in EOC cells. IL-8 is a potent proangiogenic cytokine associated with tumor growth and metastasis [12]. Furthermore, the use of beta-blockers, which inhibit the effects of norepinephrine, has been associated with prolonged survival for women with EOC in some studies [13], but not all [14].

Factors measuring particularly social isolation and depression have been found to be associated with elevated levels of norepinephrine in tumor cells among patients with EOC [15,16]. Multiple studies have shown that stress hormones could enhance EOC tumour growth [10–12] and that social isolation is associated with worse survival outcomes for patients with EOC [17]. Furthermore, high levels of anxiety and depression has been associated with the expression of β_2-adrenergic receptors in tumor tissue [18]. In addition, low social support among EOC patients is associated with elevated levels of vascular endothelial growth factor [19,20], matrix metalloproteinase 9 [20], interleukin 6 [21] and down regulated activity of natural killer cells [22]. These changes promote the tumor cells' ability to form adhesions, penetrate extracellular matrix, form new blood vessels, proliferate and metastasize [7,12,19–22]. Furthermore, high social support is associated with prolonged survival compared to those with low social support among patients with EOC [17].

In general, psychological stress and depression is suggested to impair the immune response and increase the risk for cancer initiation [23]. Concerning developing EOC, a modestly increased risk has been found to be associated with depression measured 2–4 years before EOC showing decreased risk-estimates following longer lagtime [24]. On the contrary, work-characteristics in another study were not associated with increased risk of EOC [25]. Few other studies have, however, explored the relation between psychosocial factors and the *incidence* of EOC. Based on the above-mentioned circumstances, the aim of this prospective nested case-control study was to examine whether the incidence of EOC differed between women with self-perceived low social support compared to those with self-perceived high social support.

2. Materials and methods

2.1. Cohort

Umeå University Institutional Review Board approved (Dnr 2011-362-31M) this case-control study nested within the population-based Västerbotten Intervention Programme (VIP) including 58,000 women [26,27]. The Swedish Cancer Registry was used to identify cases based on the diagnosis code from the tenth revision of the International Classification of Disease (ICD-10). Cases with EOC, fallopian tube cancer (FTC) and primary peritoneal cancer (PPC) were selected. FTC and PPC share risk factor profiles, clinical and prognostic factors as well as molecular patterns with EOC, and are therefore traditionally approached as EOC in clinical and research settings [28–30]. However, PPC has in another study been found to have a separate behaviour from EOC and FTC [31]. Both cases with invasive cancer and borderline tumors with low malignant potential were included.

In the present study, cases were selected if they, prior to diagnosis, participated in the VIP. The VIP is a community intervention programme with the primary goal to reduce cardiovascular and metabolic morbidity and mortality, integrated in primary health care routine in Västerbotten County in the northern part of Sweden [26,27]. All persons at ages 40, 50 and 60 years are invited to do a clinical examination and to participate in screening for risk factors by completing a questionnaire on health and lifestyle habits [26]. Questions concerning education, employment, physical activity (the validated Cambridge index for physical activity [32]), smoking, marital status and social support were used in the present study, as well as the measurements of weight, height and blood pressure. Criteria for inclusion were: 1) a minimum of one year between participation in the VIP and cancer diagnosis, 2) no previous cancer, including in-situ cancer, except non-melanoma skin cancer and 3) that the participants had at least one ovary left. Each case was matched to four cancer-free controls from the VIP cohort regarding age (±1 year) and date of completing the questionnaire (±1 month). Participation in the VIP took place between 1985 and 2013 and the year of EOC diagnosis ranged from 1988 to 2015. The VIP does not include data regarding all known risk factors such as hereditary risk of EOC, parity, ever use of oral contraceptive pills or hormone replacement therapy. Thus, analyses regarding those risk factors were unfortunately not possible.

2.2. Assessment of social support

In the VIP, the questionnaire on risk factors contains a modified version of the validated questionnaire Social Support (SS13) [33]. SS13 is an abbreviated version of the Interview Schedule for Social Interaction (ISSI), developed to survey different perspectives on social support in population studies [33,34]. SS13 contains questions that measure the availability of social integration (AVSI) and questions that measure the availability of attachment (AVAT) [33]. The VIP does not contain all questions from SS13 and some new questions are added. The new questions were excluded since they are not part of the validated original. Therefore, in the present study, four questions regarding the *quantity* of social support (AVSI) and six questions reflecting the *quality* of social support (AVAT) were used (Table 1).

In this study, each case was required to have at least one individually matched control during the analyses, otherwise it was excluded. Since the aim of the study was to explore the potential association between social support and EOC incidence, adequate data on social support was required to be included in the study. Individuals with >1 missing answer on AVSI and those with >2 missing answers on AVAT ($n = 14$) were excluded from analyses regarding AVSI and AVAT, respectively. To compensate for missing data for those with 1 missing answer on AVSI or 1–2 missing answers on AVAT, the mean value was calculated for each individual for AVSI and AVAT respectively.

2.3. EOC diagnosis

Data on histopathology, tumour grade and behavior (borderline or invasive cancer) was retrived from the Department of Biobank research at Umeå University and from the Regional Cancer Centre North, Umeå

Table 1
The modified version of the social support questionnaire SS13.

Availability of Social Integration (AVSI)[a]
1. How many people, with the same interests as you, do you know and have contact with?
2. How many people that you know do you meet or talk to during a normal week?
3. How many friends do you have who can come to your home at any time and feel like home? They would not care if it was unclean or if you were eating. Do not count relatives.
4. How many are there with whom you can speak openly without thinking twice?
Availability of Attachment (AVAT)
1. Is there someone special from whom you really can feel support?[b]
2. Is there someone special who feels close to you?[c]
3. Do you have someone with whom you can share your innermost feelings when you feel happy? Someone whom you feel sure will feel happy simply because you are?[b]
4. Do you have someone with whom you can share your innermost feelings and really confide in?[b]
5. Does anyone ever hold or embrace you to give comfort and support?[b]
6. Do you think people, those at home or others, really appreciate what you do for them?[d]

[a] Classification of answers: None (0 points), 1–2 people (1 point), 3–5 people (2 points), 6–10 people (3 points), 11–14 people (4 points) and > 15 (5 points).
[b] Classification of answers: No (0 points), Yes (1 point).
[c] Classification of answers: No (0 points), Yes (1 point), Not sure (1 point).
[d] Classification of answers: No (0 points), Yes (1 point), Not enough (0 points).

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