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Statins, aspirin and risk of thromboembolic events in ovarian cancer patients

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HIGHLIGHTS

- We studied the association between statins and aspirin and risk of VTEs in patients with ovarian cancer.
- Statin use was not associated with a reduced risk of VTEs in this cohort.
- Aspirin use was associated with a decreased risk of VTEs that was marginally statistically significant.

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ABSTRACT

Objectives. Studies suggest that statins and low dose aspirin reduce risk of VTEs in the general population. We aimed to study the effect of these drugs on the incidence of VTEs in patients with ovarian cancer.

Methods. Patients diagnosed with ovarian cancer between 2000 and 2011 were identified through the Clalit Health Services (CHS) chronic disease registry. Data were extracted from CHS database and from computerized pharmacy records. Use of medications was analyzed as a time dependent covariate in a Cox regression model.

Results. Of 1746 patients 175 (10%) had a VTE during a median follow up of 3.13 years. 83 patients (5.6%) had a VTE within 2 years of diagnosis of ovarian cancer. Use of chemotherapy and stage 3 and 4 at presentation were associated with an increased risk for VTEs.

Statins were used by 43.5% of the patients, and 32.3% used aspirin. Aspirin use was associated with a marginally significant reduction in incidence of VTEs within 2 years of diagnosis, HR 0.423 (95% CI 0.182–1.012, *p*-value 0.053). Statin use was not associated with risk of VTEs.

Conclusion. This is the first study looking at the effect of statins and aspirin on the incidence of VTEs in ovarian cancer patients. In our cohort, statins did not decrease the risk for a VTE and aspirin use was associated with a reduced risk which was marginally significant. Our results might be explained by use of low potency statins and by alternate mechanisms for VTE formation in cancer patients.

Introduction

Ovarian cancer patients are at increased risk of venous thromboembolic events (VTEs) [1,2]. The incidence was reported to be about 3% in women recruited to randomized trials of first line chemotherapy [1], and as high as 10% in women treated outside a clinical trial [2–4]. VTEs are associated with increased risk of death in ovarian cancer patients [5,1], and patients treated for a VTE are also at increased risk of recurrent thromboembolism and bleeding [6].

Statins are widely used to treat hypercholesterolemia. Several observational and case control studies have shown that use of statins is associated with a reduced risk for VTEs in the general population [7–12]. JUPITER was a randomized placebo controlled trial of rosuvastatin in adults with increased CRP level. Treatment with rosuvastatin decreased the incidence of symptomatic VTEs by 43% [13]. Several cohort studies did not find an association between statin use and risk of VTEs [14–16]. A recent metaanalysis of randomized trials of that used toxicity reporting to assess incidence of VTEs concluded that statins do not reduce the risk of these events [17]. The discrepancies between the different studies might be due to differences in statin strength and dose and in their design. Currently the effect of statins on VTE risk remains undetermined.

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Several mechanisms can explain the effect of statins on the risk of VTEs. Statins act by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. This leads to inhibition of the Mevalonate pathway, affecting intracellular signaling pathways, resulting in anti-inflammatory, immune-modulatory, antioxidant and antithrombotic effects [18,19] and possibly anti-cancerous effects [20–23] as well.

Low dose aspirin has been shown to reduce the risk of deep vein thrombosis and pulmonary embolism in surgical patients [24] and patients with a previous arterial occlusive event [25]. Randomized trials demonstrated that low dose aspirin reduces the risk of VTE recurrence after completion of oral anticoagulant treatment [26], and is as effective as low molecular weight heparin (LMWH) for VTE prophylaxis in multiple myeloma patients treated with thalidomide [27] or lenalidomide [28].

International guidelines do not support routine prophylactic use of anti-coagulants in ambulatory cancer patients [29]. Given their low cost and manageable safety profile, statins and aspirin could potentially serve as VTE prophylaxis in high risk patients with ovarian cancer.

Statin use was shown to be associated with a decreased risk for a VTE in hospitalized patients with various solid tumors [30]. Our aim was to study the association between statins and aspirin and the incidence of VTEs in patients with ovarian cancer.

Methods

Study population

Patients aged 18–90 years that were diagnosed with invasive epithelial ovarian cancer in Israel between 2000 and 2011 were identified through Clalit Health Services (CHS) chronic disease registry. Health care coverage in Israel is mandatory and is provided by four nonprofit organizations. Thus, all study participants had a similar basic health insurance plan and similar access to health services. Patients who took warfarin or LMWH for 3 months or longer were excluded. Patients were followed until study termination, death or diagnosis of VTE. The Institutional review board of Carmel Medical Center, Haifa, Israel, approved all procedures.

Drug exposure data

The use of statins, aspirin, warfarin and LMWH was determined on the basis of CHS pharmacy records that were available for all study participants. Chemotherapy use was determined on the basis of CHS pharmacy records and hospital and day-care admission data. The pharmacy records of CHS are a reliable source of use of medication data as co-payment for drugs is very low in Israel, making it unlikely that prescription medications were purchased in private, non-CHS pharmacies or as over the counter medications. Detailed prescription information enabled us to assess drug exposure over time and evaluate the risk of VTEs in relation to the time course of drug exposure.

For the purpose of calculating exact exposure period to the drugs of interest we considered patients to be on statins until 1 month and on aspirin 1 week from the end of their last prescription. Chemotherapy exposure duration was defined as 1 month after each treatment day to avoid artificial gaps in treatment continuity caused by cycle delays.

Additional data

Diagnoses are coded based on tumor origin and histological subtype and stage at diagnosis is recorded as well. The Charlson comorbidity index predicts 10 year mortality for people with a wide range of medical conditions [31]. Comorbidities prior to the time of ovarian cancer diagnoses were retrieved from the CHS database. Patients were divided into two groups: Charlson index 0–2 vs 3 or more.

End points

The occurrence of deep vein thrombosis and/or pulmonary embolism was determined from the CHS database. Diagnoses assigned in the inpatient and outpatient setting are inserted to the database through hospital discharge records and by physicians working in the community setting. These diagnoses are coded and can thus be reliably retrieved. Patients were considered to have had an event if diagnosed with lower or upper extremity deep vein thrombosis and/or pulmonary embolism (ICD codes: 4511, 4442, 4512, 41511, 4151, 4511, 45111, 45119, 45181, 45340–2, 45184, 4532). Diagnoses of superficial vein thrombosis were not considered a VTE.

Statistical analysis

Statistical analysis was performed using SPSS (v 18). The use of medications was analyzed as a time dependent covariate in a Cox regression model. The incidence of events during drug exposure for the whole study population was compared to the incidence of events occurring at times without drug exposure.

Results

1743 ovarian cancer patients were included in the study. Median follow up was 3.15 years, probably due to a high mortality rate in patients with ovarian cancer. Median age was 61.8 years. 168 (9.6%) patients had stage 1 disease at diagnosis, 318 (18.2%) had stage 2 disease, 981 (56.3%) had stage 3 or 4 and for 276 (15.8%) information regarding stage was missing.

759 (43.5%) patients used statins at any time during follow up and 563 (32.3%) used aspirin. Of aspirin users, 91% took 75–100 mg per day. 1532 (87.9%) were treated with chemotherapy. Of 981 patients with stage III and IV disease, 291 used statins and 387 used aspirin.

175 (10%) patients had a VTE during the follow up period. 83 (5.6%) patients had a VTE within 2 years of ovarian cancer diagnosis. The characteristics of patients that did and did not have a VTE are presented in Table 1.

We analyzed the risk factors for VTEs within 2 years of diagnosis and throughout follow up. Factors included in the analysis were age, Charlson comorbidity Index, tumor stage, use of chemotherapy and statin and aspirin use. As shown in Table 2, on multivariate analysis only stage at diagnosis and chemotherapy use were associated with the risk for a VTE within 2 years of diagnosis and throughout follow up. The percentages of patients with VTEs according to stage at diagnosis are shown in Table 3.

30 patients had a VTE prior to diagnosis of ovarian cancer but were not treated by LMWH or warfarin and were thus included in the cohort. None of these patients had a VTE during follow up.

Statin use was not associated with a reduced risk for VTEs within 2 years of diagnosis and throughout follow up. Use of aspirin was associated with a reduced risk of VTEs within 2 years of diagnosis

Table 1
Characteristics of study participants. VTE—venous thromboembolic events.

	With VTE (%)	Without VTE
Statins	71 (40.6)	688 (43.9)
Aspirin	51 (29.1)	512 (31.7)
Chemotherapy	171 (97.7)	1361 (86.6)
Stage		
1	12 (7.7)	156 (11.9)
2	31 (19.9)	287 (21.9)
3 + 4	113 (64.6)	868 (55.4)
missing	19 (10.9)	257 (16.4)
Charlson index		
0–2	92 (52.6)	769 (49)
≥3	83 (47.4)	799 (51)
Age (median)	62.8	61.5