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Full length article

The impact of histological subtype in developing both ovarian and endometrial cancer: A longstanding nationwide incidence study

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ABSTRACT

Objectives: To estimate the incidence of ovarian cancer (OC) and endometrial cancer (EC) separately, as well as double cancers diagnosed in the same calendar year, and to relate the occurrences to histological subtype.

Study design: All cases of epithelial OC and EC diagnosed in the Netherlands in 1989–2009 were related to population data. Histologically specific associations were made using the ratio of observed and expected incidence numbers, calculated with age-specific incidence rates.

Results: 25,489 OC and 32,729 EC were analyzed, and 649 OC/EC. Life-time risks for OC and EC were 1.8% and 2.4%. Among OC, adenocarcinoma (18%) and serous cancers (33%) were the most prevalent subtypes. In EC, adenocarcinoma (39%) and endometrioid cancer (37%) were highest, with hardly any serous cancers. The observed incidence of OC/EC was 50-fold higher than expected (95% CI, 46–54). For patients aged <55 years, the O/E ratio was 274, for the elderly 32, both findings are significant. Of the 2345 OC endometrioid subtype, 294 had EC (12.5%), whereas 1.1 was expected. In EC patients, no particular histological subtype was distinguished with a highly elevated occurrence of OC. The 680 serous EC patients had 11 double cancers (1.6%), of which 8 with the ovarian serous subtype.

Conclusion: Strong relationships exist between malignancies in the ovary and a second primary malignancy in the endometrium, especially for the endometrioid subtype of ovarian cancer. Viewed from the endometrial site, no special subtype was noted, and the influence of endometrial serous adenocarcinoma in developing serous OC is not plausible.

Introduction

In gynecologic oncology, the diagnosis of both an ovarian cancer (OC) and endometrial cancer (EC) is not uncommon [1]. The possible occurrence of OC within a short time frame of having EC, and vice versa, directs diagnosis, prognosis, treatment and post-treatment surveillance. The occurrence of these double primary cancers, OC/EC, is also an important object of histopathological investigations on carcinogenesis. Insights into the carcinogenesis of these tumors not only benefit from molecular studies, but also from epidemiological studies that use frequency-type data from patients. The most frequently observed synchronous primary cancers of the female genital tract are found among patients diagnosed with ovarian and endometrial cancers [2]. The specific pathogenic pathways, however, remain unclear [3], especially in those patients with a primary carcinoma in the ovary, as well as from the endometrium side.

Previous epidemiological studies suggest that the major histological subtypes of epithelial cancer have different risk factor profiles; however, no known prospective epidemiological study has systematically examined differences in risk by subtype [4]. The histology of the heterogeneous group of ovarian neoplasms comprises serous, mucinous, endometrioid, clear cell transitional, and squamous cell subtypes [5–9]. Surprisingly, none of these histological subtypes are found in the normal ovary, and the development of ovarian cancer has long been attributed to “müllerian neometaplasia” of the ovarian epithelium [8]. Based on histopathology, immunohistochemistry and molecular genetics, these five main cancer types have also been distinguished based on epidemiological, morphological and genetic factors [10,11], patterns of tumor spread, precursor lesions [12–14], molecular events during oncogenesis, prognosis, and on their response to chemotherapy [8].

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The endometrioid subtype of ovarian cancer is the main form with a concurrent malignancy in the endometrium [5]. It is possible that the endometrioid ovarian cancer subtype is specifically involved in the development of the second primary cancer in the endometrium in the same patient. Therefore, we investigated the influence and development of carcinoma subtypes in patients with a primary carcinoma in the ovary, but also studied the occurrence of second primaries in the ovary among patients with endometrial cancer [15–18].

Materials and methods

Data sources

We received data from the population-based Netherlands Cancer Registry (NCR): 25,489 patients with primary epithelial ovarian cancer and 32,729 with primary epithelial endometrial cancer, diagnosed in the Netherlands between 1989 and 2009 [19,20]. The age-specific population data came from Statistics Netherlands.

Incidence study

The ovarian and endometrial malignancies were classified into 5-year categories of age at diagnosis. For histological subtype, we followed *The International Classification of Diseases for Oncology (ICD-O WHO)*: adenocarcinoma (value label 8140), serous carcinoma (label 8441, 8460, 8461), endometrioid carcinoma (8380), mucinous carcinoma (8470, 8480), clear cell carcinoma (8310), papillary adenocarcinoma (8260) and borderline malignant (8444, 8451, 8462, 8463, 8472, and 8473 [21].

Incidence rates of ovarian cancer, endometrial cancer and double cancer, defined as ovarian and endometrial cancer diagnosed in the same calendar year, were calculated and displayed for level of occurrence, age-shape, and age-peak. Similarly, graphs were constructed for the main histological subtypes.

Statistical analysis

Associations of subtypes from both sites were quantified by relating the observed number of double cancers to the expected number. Expected numbers were calculated by multiplying age-specific incidence rates of ovarian cancer of the Dutch population with the corresponding age-specific absolute numbers of patients with endometrial cancer, and of endometrial cancer in patients with ovarian cancer. Observed (O) numbers were divided by the expected (E) numbers to obtain O/E ratios, and 95% confidence intervals (CI) were calculated with the method originated by Byar [22]. Analyses were completed for all ages, and separately for the age groups <55 year and 55 or higher.

Results

Incidence of primary cancers

Between 1989–2009, a total of 649 OC/EC were noted for 25,489 diagnosed epithelial OC and 32,729 epithelial EC. Fig. 1 shows the incidence rates of OC and EC per 100,000 person-years (PY), and per 1,000,000 PY for OC/EC. Up to the age of 40, the incidence rate for OC and EC is relatively low. The turning point is around 40–44 year, at $20/10^5$ PY, where levels begin to increase steadily, especially for EC. The incidence flattens out in the age-band of 65–75, at $50/10^5$ PY and $70/10^5$ PY respectively, with a small after-peak at age 80–84. Taking the incidence rates over the continuum of age, the woman's lifetime risk for OC is 1.8 per cent, and 2.4 per cent for EC.

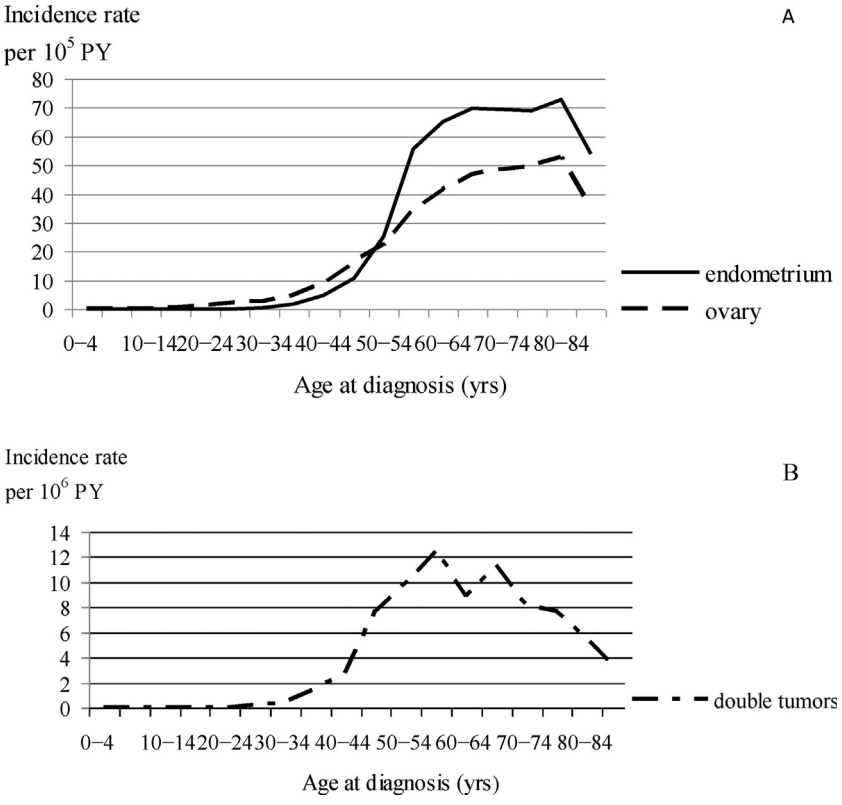

Fig. 1. Age-specific incidence rate of ovarian and endometrial cancer (panel A) and double cancer (panel B) in the Netherlands in the period 1989 –2009.
PY = person-year