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Risk of cancer among women with polycystic ovary syndrome: A Danish cohort study

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HIGHLIGHTS

- Cancer risk among 12,070 women with polycystic ovary syndrome (PCOS) was studied.
- We confirmed prior findings of an excess of endometrial cancer in PCOS.
- No excess of breast or ovarian cancer was observed.
- Among sites not studied before, we saw excesses of kidney, colon and brain cancer.

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ABSTRACT

Objective. To assess the association between polycystic ovary syndrome (PCOS) and cancer, especially of the endometrium, breast and ovary.

Methods. The Danish National Patient Register was used to identify 12,070 in- and outpatients in whom PCOS was diagnosed when they were aged 9–49 years during 1977–2012. Using the Danish Cancer Registry, we followed the cohort through 2012 and compared the women's cancer incidence with that of the general Danish female population by means of standardized incidence ratios (SIRs).

Results. Cancer was diagnosed in 279 women with PCOS (SIR = 1.19; 95% CI = 1.06–1.34). We found an almost fourfold increased risk for endometrial cancer (numbers observed (N) = 16, SIR = 3.9; 95% CI = 2.2–6.3), the large majority of cases being type 1 (N = 14, SIR = 4.7; 95% CI = 2.6–7.9). We found no association between PCOS and breast (N = 59, SIR = 1.1; 95% CI = 0.8–1.4) or ovarian cancer (N = 10, SIR = 1.8; 95% CI = 0.8–3.2); however, significantly increased risks were found for kidney, colon and brain cancers.

Conclusion. The results of this large cohort study support those of case–control studies showing that women with PCOS are at increased risk for endometrial cancer, whereas their risks for breast and ovarian cancer are similar to those of women in the general population. Our finding that women with PCOS also are at increased risk for cancers of the kidney, colon and brain requires further study.

Introduction

Polycystic ovary syndrome (PCOS) is one of the commonest endocrine illnesses in women of reproductive age. It is characterized by chronic oligo- or anovulation, hyperandrogenism and polycystic ovaries [1] and is associated with several long-term health consequences, such as infertility, obesity, hypertension, dyslipidemia, insulin resistance and type II diabetes mellitus [1–3]. The prevalence of PCOS among western European women of reproductive age is reported to range from 11% to 21% when using the Rotterdam criteria from 2003 [4–6].

Nulliparity, obesity and prolonged unopposed estrogen are some of the health consequences of PCOS that are associated with cancer [7–10]. The authors of a recent meta-analysis found a significant three-fold increase in risk for endometrial cancer among women with PCOS but no significant excess risks for either breast or ovarian cancer [11]. The analyses were, however, based on few studies (five of endometrial cancer, three each of breast cancer and ovarian cancer), most of which were case–control studies with small sample sizes, and the diagnosis of PCOS was self-reported in most studies. Thus, although patients with PCOS are often cited to be at increased risk for endometrial cancer, the evidence to support this claim is relatively weak.

Large cohort studies are warranted of the entire spectrum of cancer in women with PCOS and of specific associations between PCOS and endometrial, breast and ovarian cancer. Therefore, we investigated the

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risk for cancer in a cohort of Danish women with PCOS, identified in the Danish National Patient Register during 1977–2012, and followed for cancer in the Danish Cancer Registry through 2012.

Material and methods

In this registry-based cohort study, we identified women who had received a main or a secondary diagnosis of PCOS (Danish version of the International Classification of Diseases (ICD) ICD-8 = 256.90 during 1977–1993, and ICD-10 = E28.2 during 1994–2012) and were registered in the Danish National Patient Register [12] during 1977–2012. This register contains records of virtually all hospitalizations since 1977, and outpatient visits since 1995 on somatic wards in Denmark. For each hospital contact, the personal identification number of the patient, the dates of admission or first visit, the date of discharge or last visit, diagnoses (ICD-8 or ICD-10) and every surgical procedure performed during the contact are registered; surgical procedures are recorded and classified according to the Danish Classification of Surgical Procedures and Therapies. We included diagnoses from hospitalizations as well as outpatient visits in our study. The women had to be aged 9–49 years at first admission or visit for PCOS, as it previously has been recognized that the syndrome can be diagnosed as early as the age of 9 [13] and because it is not clear whether PCOS after menopause has a specific phenotype [3]. A total of 12,131 women with PCOS fulfilled these eligibility criteria.

Each resident of Denmark is assigned a unique personal identification number at birth, which contains the date of birth and sex. These identification numbers are used throughout the Danish society, including in all health registers, and ensure unambiguous linkage between the various registries. Using the personal identification numbers as key identifiers, we linked the cohort of women with PCOS to the Central Population Register to obtain information on death and emigration. We excluded 47 (0.4%) women with an invalid identification number and 14 (0.1%) who had died or emigrated before the diagnosis of PCOS, leaving 12,070 for analysis.

Identifying cancer

The identification numbers of all women with PCOS were linked to the Danish Cancer Registry, which was established in 1943. Until 2003, registration was based on notification forms from hospitals, general practitioners and specialists [14]. Since 2004, the Registry has been based on recordings in other health registries, mainly the National Patient Register. The obligation to notify the Cancer Registry applies to all malignant neoplasms as well as histologically benign tumors of the central nervous system and papillomas of the urinary tract. Computerized checks are run within the Registry to identify logical errors and rare combinations, which are reviewed manually. The proportion of microscopically confirmed cases has furthermore increased over the years, and the proportion based on death certificates alone has decreased [14].

Women with PCOS were followed for cancer from the date of their first admission or visit for PCOS until emigration, death or December 31, 2012, whichever came first. Cancer was diagnosed in 105 women before or on the same date as the diagnosis of PCOS; six of these had endometrial cancer (five <1 year before and one ≥1 year before), three had breast cancer (all diagnosed <1 year before) and three had ovarian cancer (two <1 year before and one ≥1 year before). Pituitary tumors were diagnosed in 12 women before the diagnosis of PCOS (four <1 year before and eight ≥1 year before) (data not shown). These malignancies were not included in the analyses, but the women remained in the cohort as they were at risk for other malignancies.

Statistical analysis

Standardized incidence ratios (SIRs), with corresponding 95% confidence intervals (CIs), were calculated as the ratio of the observed number of cancer cases in the cohort to the expected number. The latter was calculated by multiplying national cancer incidence rates for females in 5-year age groups and calendar periods by the number of person-years at risk for the study cohort in corresponding strata and summing up these strata. The SIRs were based on the assumption that the observed number of cancer cases in a specific category followed a Poisson distribution [15], and the confidence limits were calculated by Byar's approximation [16]. The analyses were stratified on age at first contact for PCOS (9–29, 30–39 and 40–49 years), age at cancer (<50 and ≥50 years), time since PCOS (<1, 1–4, 5–9 and ≥10 years), patient type (in- or outpatients) and calendar year at first PCOS (<1995, 1995–2003 and 2004–2012) for selected cancer types. The excess absolute risk was calculated as the observed minus the expected rate per 100,000 person-years.

Increased body mass index (BMI) is recognized as an important risk factor for several cancers in adults, as it affects the levels of numerous hormones and growth factors [7,9]. As a high prevalence of obesity has been reported among women with PCOS [1,3], we categorized cancer outcomes into (1) cancers convincingly associated with BMI, (2) cancers possibly associated with BMI and (3) other [7,9,17].

We classified endometrial cancer as type 1 (ICD-O-3 morphology codes 81403, 81433, 82103, 82303, 83803, 83813, 84303, 84703, 84803, 84813, 85603 and 85703) and type 2 (80203, 80213, 80503, 82463, 82603, 83103, 84403, 84413, 84503, 84603, 84613, 89333, 89343 and 89503) according to a slightly modified version of the classification by Evans et al. [18] and as other endometrial cancers (all other morphology codes included as endometrial cancer). We categorized the brain tumors as pituitary and non-pituitary. Pituitary tumors were defined as ICD-7 = 195.3 (before 1978) and as ICD-O-3 topography code C75.1 (in 1978–2012).

Results

The cohort consisted of 12,070 women with PCOS (Table 1). Almost one third were aged 15–24 years at the date of first admission or visit for PCOS, and approximately 50% were aged 25–34 years. The majority of women (85%) were identified from outpatient records. The numbers of both in- and outpatients with PCOS increased markedly during the study period. The cohort was followed for a total of 91,036 person-years, with a median follow-up time of 5.7 years (10th percentile, 1.0 years; 90th percentile, 16.1 years).

Table 1
Characteristics of 12,070 women with polycystic ovary syndrome (PCOS) diagnosed during 1977–2012 in Denmark.

Characteristic	Number of women	(%)
Age at first PCOS (years)		
9–14	183	(2)
15–19	1307	(11)
20–24	2592	(21)
25–29	3781	(31)
30–34	2502	(21)
35–39	1215	(10)
40–44	363	(3)
45–49	127	(1)
Inpatient		
Period of first PCOS		
1977–1985	366	(3)
1986–1994	322	(3)
1995–2003	438	(4)
2004–2012	667	(6)
Outpatient		
Period of first PCOS		
<1995[a]	123	(1)
1995–2003	2300	(19)
2004–2012	7854	(65)

[a] The Danish National Patient Register started recording outpatient visits with dates of last visit in 1995 or later. As we used dates of first visit in the study, some of these were before 1995.