Breast Cancer Research and Treatment (2019) 178:199–205
https://doi.org/10.1007/s10549-019-05369-8

EPIDEMIOLOGY

Risk of breast cancer among women with benign ovarian tumors: a Danish nationwide cohort study

Mathilde Gottschau[1] · Allan Jensen[1] · Kristian Reinholdt[1] · Sonia Guleria[1] · Christian Munk[1] · Lene Mellemkjær[1] · Susanne K. Kjær[1,2]

Received: 16 July 2019 / Accepted: 17 July 2019 / Published online: 30 July 2019

Abstract

Purpose To assess the association between benign ovarian tumors and subsequent risk of breast cancer, and to examine this association according to type of benign ovarian tumors.

Methods This nationwide cohort study comprised all Danish women diagnosed with a benign ovarian tumor during 1978–2016 ($n = 158{,}221$) identified through the Danish National Patient Register. The cohort was linked to the Danish Cancer Registry to identify all cases of breast cancer, and standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated.

Results Overall, women with a benign ovarian tumor were at significantly increased risk of breast cancer. The risk was confined to women with a solid ovarian tumor (SIR 1.09; 95% CI 1.05–1.13), particularly in women ≥ 50 years at benign tumor diagnosis (SIR 1.19; 95% CI 1.12–1.26). The risk remained increased up to 20 years or more after the diagnosis of a solid ovarian tumor (SIR 1.11; 95% CI 1.04–1.18), and women with a solid tumor were at increased risk of ductal, lobular, and other types of breast cancer, although most consistent for the lobular subtype. For cystic tumors, this association was confined to ductal breast cancer in women with the tumor diagnosed at age ≥ 50 years.

Conclusions Women with a benign ovarian tumor were at increased risk of breast cancer. This association was largely confined to women with a solid ovarian tumor, and the excess risk was present 20 years or more after the ovarian tumor diagnosis. The underlying mechanism is unknown and should be investigated further.

Keywords Benign ovarian tumors · Ovarian cysts · Breast cancer · Cohort study · Denmark

Introduction

Breast cancer is the most common type of malignancy among women worldwide [1]. In Denmark, the incidence has increased since the 1960s, but in recent years, it appears that a steadier state has been reached [2]. Today, nearly 5000 women are diagnosed with breast cancer each year. The mortality in Denmark has been declining since the 1990s [2], which is assumed to be the result of mammography screening and improved treatment [3].

✉ Susanne K. Kjær
susanne@cancer.dk

[1] Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen, Denmark

[2] Department of Gynecology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

Invasive breast cancer is a heterogeneous group of tumors with ductal adenocarcinomas as the most common histopathologic subtype, followed by lobular carcinomas [4]. Breast cancer is referred to as an estrogen-dependent cancer with risk factors such as early age at menarche, later age at menopause, nulliparity, late age at first birth, exogenous hormone use, obesity, and alcohol [5]. Although differences in risk factors for ductal and lobular breast cancer are not well investigated, it has been suggested that lobular breast cancer is more strongly related to estrogen exposure [6].

Benign ovarian tumors may most often be cystic tumors but can also be a solid ovarian tumor [7]. The etiology of benign ovarian tumors is not fully understood, but it has been proposed that risk factors may differ among these two subtypes [8]. Data on the frequency of benign ovarian tumors are sparse, but a study from the US reported that 8.3% of 15,735 postmenopausal women enrolled in a screening trial for lung, colorectal, and ovarian cancer had

at least one simple cyst detected on transvaginal ultrasound performed 1 year after a normal scan [9]. Furthermore, a small Danish study found a prevalence of 7% of benign ovarian cysts in 428 gynecologic healthy premenopausal women [10]. Benign ovarian tumors have been associated with irregular menstrual cycles and infertility and are suspected to be related to altered estrogen levels [8, 11, 12]. Due to these hormonal abnormalities, benign ovarian tumors have been hypothesized to be associated with breast cancer.

Previous studies on the association between benign ovarian tumors and breast cancer are inconsistent. Whereas some studies find no association [13–17] or a protective effect [18–21], others report an indication of increased risk of breast cancer among women with a benign ovarian tumor [22, 23]. However, the majority of studies are case–control studies based on self-reported information from interviews. Furthermore, many studies only examine the association with ovarian cysts [13, 14, 18–21, 23] and others do not distinguish between ovarian cysts and solid tumors [15, 17], which potentially may have an impact on the association.

In this nationwide, register-based cohort study, we investigated the association between benign ovarian tumors and breast cancer, and more specifically, we wanted to examine whether this association differed according to histologic subtype.

Methods

We identified all women living in Denmark with a diagnosis of a benign ovarian tumor registered in the Danish National Patient Register [24] during 1978–2016. The National Patient Register was established in 1977, comprising information on virtually all hospitalizations since 1977 as well as emergency and outpatient visits since 1995 from somatic wards in Denmark. All records in the National Patient Register contain information on the unique personal identification number (CPR-number) of the patient, date of admission or first visit, diagnosis codes (Danish version of the International Classification of Diseases 8th edition (ICD-8) during 1977–1993 and 10th edition (ICD-10) after 1994), and surgical procedures performed during the hospitalization/outpatient contact. Classification of surgical procedures was changed in 1996 from the Danish Classification of Surgical Procedures and Therapies to the Nordic Classification of Surgical Procedures. In this study, we included women aged 15 years and older with a main or a secondary diagnosis of benign ovarian tumors received as either part of a hospitalization or an outpatient visit. Benign tumors were classified as either solid (ICD-8 = 220.99 and ICD-10 = D27.0, D27.1, D27.2, D27.8, D27.9) or cystic (ICD-8 = 615.20, 615.21, 615.22, 615.28, 615.29 and ICD-10 = N83.0, N83.1, N83.2).

By using the unique CPR-number that every citizen of Denmark is assigned at birth or at immigration containing information on date of birth and gender, women with a benign ovarian tumor were linked to the Danish Civil Registration System [25] to obtain information on deaths and emigrations.

Identification of cancer

All women in the cohort were linked to the Danish Cancer Registry [26] to obtain information on incident cancer cases. This nationwide registry was established in 1943 and contains information on all incident cases of malignant neoplasms. In 2004 registration by notification forms from hospitals, general practitioners and specialists were replaced by recordings from several Danish health registries, mainly the National Patient Register. All women in the cohort with a breast cancer diagnosis were identified according to ICD-10 = C50. Codes of the third edition of the International Classification of Diseases for Oncology (ICD-O-3) are used in the Cancer Registry for tumors diagnosed from 1978. Using morphology codes of ICD-O-3, breast cancers were classified as ductal (85003, 80223, 85013, 85213, 85413, 85403, 85103, 82113, 80103, 80123, 80133, 80203, 80213, 80323, 80463, 80503, 81403, 81413, 82113, 82303, 82463), lobular (85203, 84903, 80373), and other breast cancer types (all other morphology codes with a fifth digit of 3).

Women with a benign ovarian tumor were followed for cancer from their first admission or outpatient visit and until emigration, death or end of this study (December 31, 2016), whichever came first.

Statistical analyses

We assessed the association between being diagnosed with a benign ovarian tumor (overall and the two subtypes) and subsequent breast cancer (overall and three subtypes) by using standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs), calculated as the ratio of the observed number of cancer cases in the cohort to the expected number. The latter was calculated by multiplying accumulated person-years at risk by national cancer incidence rates for females in 5-year age groups and calendar periods. The SIRs were calculated on the assumption that the observed number of the specific cancer cases followed a Poisson distribution [27] and the confidence intervals were calculated by Byar's approximation [28].

The overall analyses were carried out with and without the first year of follow-up. In order to be sure to avoid prevalent cases of breast cancer, the subsequent stratified analyses excluded the first year of follow-up. We stratified the analyses according to age at first benign ovarian tumor (< 30 years, 30–39 years, 40–49 years, and ≥ 50 years) and

time since benign ovarian tumor (1–4 years, 5–9 years, 10–19 years, and ≥ 20 years). We performed all statistical analyses by using SAS Enterprise Guide, version 7.1 (SAS institute, Cary, NC, USA).

Results

The study cohort consisted of 158,221 women with a benign ovarian tumor and we followed these women for a total of 2,379,313 person-years (Table 1). These numbers were reduced to 150,651 women and 2,224,864 person-years after exclusion of the first year of follow-up.

A total of 5427 women were diagnosed with breast cancer during follow-up (5152 women after exclusion of the first year of follow-up). Overall, we found a significantly increased risk of breast cancer among women with benign ovarian tumors (Table 2), with no marked difference between estimates for the total follow-up period and after exclusion of the first year of follow-up (SIR 1.06; 95% CI 1.03–1.09 and SIR 1.05; 95% CI 1.02–1.08, respectively). When looking at the two histologic subtypes of ovarian tumors, an association was only seen for women with a solid tumor (SIR 1.09; 95% CI 1.05–1.13).

Table 1 Characteristics of women with benign ovarian tumors

Characteristics	Study cohort
Number of women with benign ovarian tumors	158,221
Solid tumors	73,872
Cystic tumors	84,349
First year of follow-up excluded	
Number of women with benign ovarian tumors	150,651
Solid tumors	71,198
Cystic tumors	79,453
Age at first benign ovarian tumor diagnosis	
Mean (10–90 pctl)	42.4 years (23.0–67.0)
Age at first cancer diagnosis	
Mean (10–90 pctl)	63.1 years (45.8–80.4)

Table 3 shows the risk estimates for overall breast cancer among women with benign ovarian tumors (overall and subtypes) when stratified according to age at and years of follow-up after a benign ovarian tumor diagnosis. For solid ovarian tumors, we found an increased risk of breast cancer that was significant ≥ 20 years after the ovarian tumor diagnosis (SIR 1.11; 95% CI 1.04–1.18). In contrast, we did not find any statistically significant association for breast cancer in any of the time intervals following a benign cystic ovarian tumor. When looking at age at first benign ovarian tumor, we found a statistically significant increased risk of breast cancer among women aged ≥ 50 years when diagnosed with all benign ovarian tumors (SIR 1.15; 95% CI 1.09–1.20). However, when looking at type of ovarian tumor, this applied mostly to women with a solid tumor, and only to a lesser extent to women with a cystic tumor (SIR 1.19; 95% CI 1.12–1.26 and SIR 1.07; 95% CI 0.99–1.15, respectively).

We also looked at the risk of different histologic types of breast cancer following a diagnosis of benign ovarian tumors (Table 4). In women with a solid ovarian tumor, we found increased risks for ductal, lobular, and other types of breast cancer, which persisted through 20 years or more after the ovarian tumor diagnosis, although most consistent for lobular breast cancer. For cystic tumors, the only statistically significant observation was a decreased risk of other types of breast cancer 1–4 years after diagnosis with SIR 0.65 (95% CI 0.46–0.88).

When looking at age at first benign ovarian tumor, we found that following a solid ovarian tumor, the risk was significantly increased for both ductal and lobular breast cancer among women aged ≥ 50 years, and for lobular breast cancer an increased risk was also seen among women aged 40–49 years at diagnosis (SIR 1.21–1.30, Table 4). For cystic tumors, the risk was also increased for both types of breast cancer in women aged ≥ 50 years at first ovarian tumor diagnosis; however, only the association with ductal breast cancer reached statistical significance (SIR 1.13; 95% CI 1.03–1.23). For other types of breast cancer, we observed no increased risk associated with older age at first benign ovarian tumor; in contrast, the risk was in fact significantly decreased in women aged ≥ 50 years at first cystic ovarian tumor diagnosis (SIR 0.79; 95% CI 0.62–0.98).

Table 2 Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) with 95% confidence intervals (95% CIs) for overall breast cancer among women with benign ovarian tumors in Denmark, during 1978–2016

	Total follow-up period				≥ 1 year after first benign ovarian tumor diagnosis			
	Person-years	Obs	Exp	SIR (95% CI)	Person-years	Obs	Exp	SIR (95% CI)
All benign ovarian tumors	2,379,313.2	5427	5109.1	1.06 (1.03–1.09)	2,224,787.0	5152	4892.1	1.05 (1.02–1.08)
Solid tumors	1,308,159.4	3260	2988.8	1.09 (1.05–1.13)	1,235,684.3	3138	2880.9	1.09 (1.05–1.13)
Cystic tumors	1,071,153.8	2167	2120.3	1.02 (0.98–1.07)	989,102.8	2014	2011.2	1.00 (0.96–1.05)

Table 3 Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for overall breast cancer among women with benign ovarian tumors according to age at first benign ovarian tumor diagnosis and time since first benign ovarian tumor diagnosis

	All breast cancers		
	Obs	Exp	SIR (95% CI)
Time since first benign ovarian tumor (years)			
All tumors			
1–4	877	837.0	1.05 (0.98-1.12)
5–9	1,085	977.9	1.11 (1.04–1.18)
10–19	1,696	1,655.6	1.02 (0.98–1.07)
≥ 20	1,494	1,421.7	1.05 (1.00–1.11)
Solid tumors			
1–4	467	433.8	1.08 (0.98–1.18)
5–9	623	538.8	1.16 (1.07–1.25)
10–19	1,027	984.6	1.04 (0.98–1.11)
≥ 20	1,021	923.7	1.11 (1.04–1.18)
Cystic tumors			
1–4	410	403.2	1.02 (0.92–1.12)
5–9	462	439.1	1.05 (0.96–1.15)
10–19	669	671.0	1.00 (0.92–1.08)
≥ 20	473	498.0	0.95 (0.87–1.04)
Age at first benign ovarian tumor (years)			
All tumors			
< 30	589	604.2	0.97 (0.90–1.06)
30–39	1,168	1,175.7	0.99 (0.94–1.05)
40–49	1.529	1,483.8	1.03 (0.98–1.08)
≥ 50	1,866	1,628.5	1.15 (1.09–1.20)
Solid tumors			
< 30	352	353.9	0.99 (0.89–1.10)
30–39	670	658.8	1.02 (0.94–1.10)
40–49	884	833.1	1.06 (0.99–1.13)
≥ 50	1,232	1,035.1	1.19 (1.12–1.26)
Cystic tumors			
< 30	237	250.3	0.95 (0.83–1.08)
30–39	498	516.8	0.96 (0.88–1.05)
40–49	645	650.7	0.99 (0.92–1.07)
≥ 50	634	593.4	1.07 (0.99–1.15)

First year of follow-up is excluded

Discussion

In this register-based cohort study with more than 150,000 Danish women with a benign ovarian tumor, we find an 11% increased risk of breast cancer ≥ 20 years after diagnosis of a solid ovarian tumor, and a 19% increase for women diagnosed with a solid tumor at age ≥ 50 years. The risk remained elevated for all three subtypes of breast cancer (ductal, lobular , and other breast cancer types). For cystic ovarian tumors, we did not find an overall association, although we did observe an increased risk of ductal and lobular breast cancer in women aged ≥ 50 years at first benign ovarian tumor diagnosis, however, only significant for ductal breast cancer.

To our knowledge, only one previous study investigated the risk of breast cancer in women with solid and cystic benign ovarian tumors separately [16]. In that study, the authors found no association with breast cancer for neither type of benign ovarian tumors in women who had undergone hysterectomy and/or oophorectomy for benign conditions such as bleeding disorders, endometriosis, ovarian cysts/benign neoplasms. or other indications. One previous case–control study from Korea [22] found an increased risk of breast cancer with OR 1.70 (95% CI 1.23–2.35); however, the exposure in this study was defined as ovarian disease without further information. Most previous studies have only investigated the risk of breast cancer in women with ovarian cysts. In alignment with our results, two studies found no association between ovarian cysts and breast cancer [13, 14], whereas one case–control study found an increased risk of breast cancer [23]. In the latter study, however, women were categorized with ovarian cysts only if they had undergone a self-reported surgery for this condition, which may affect the results, potentially making them less generalizable to all women with a benign ovarian tumor. Opposed to these results, four previous case–control studies found decreased risks of breast cancer in women with ovarian cysts [18–21]. However, all four studies were based on self-reported information on ovarian cysts, in one of the studies, the authors reported increased risk of breast cancer confined to women with ovarian ablation for ovarian cysts [21], and another study was hospital-based [20].

Our finding of an increased risk of overall breast cancer among women with solid benign ovarian tumors but not cystic ovarian tumors may be due to differences in the etiology between the two ovarian tumor types; however, this was not well investigated. It is also possible that some of the increased breast cancer risk among women with solid benign ovarian tumors may be due to genetic changes such as BRCA mutations, which increase risk for both ovarian and breast cancers in women. However, in Denmark the prevalence of BRCA mutations is approximately 6% among women with ovarian cancer [29], and is reported to be even lower among the general Scandinavian female population [30]. Therefore, it is less likely that the risk estimated in this study may entirely be explained by such mutations. Furthermore, some women with ovarian cysts may have polycystic ovary syndrome (PCOS), characterized by chronic menstrual irregularities, hyperandrogenism, and polycystic ovaries [31], which we were not able to adjust for in our analyses. It is unknown whether these women have another risk profile than women with ovarian cysts only; however, previous studies did not find any association between PCOS

Table 4 Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) with 95% confidence intervals (95% CIs) for various subtypes of breast cancer among women with benign ovarian tumors according to time since first benign ovarian tumor diagnosis and age at first benign ovarian tumor diagnosis

	Ductal breast cancer			Lobular breast cancer			Other types of breast cancer		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Overall									
All benign ovarian tumors	3,773	3,571.1	1.06 (1.02–1.09)	658	578.1	1.14 (1.05–1.23)	721	742.9	0.97 (0.90–1.04)
Solid tumors	2,254	2,085.9	1.08 (1.04–1.13)	412	344.5	1.20 (1.08–1.32)	472	450.5	1.05 (0.96–1.15)
Cystic tumors	1,519	1,485.2	1.02 (0.97–1.08)	246	233.5	1.05 (0.93–1.19)	249	292.4	0.85 (0.75–0.96)
Time since first benign ovarian tumor (years)									
Solid tumors									
1–4	341	312.1	1.09 (0.98–1.21)	58	49.2	1.18 (0.90–1.52)	68	72.5	0.94 (0.73–1.19)
5–9	445	392.4	1.13 (1.03–1.24)	77	62.9	1.22 (0.97–1.53)	101	83.4	1.21 (0.99–1.47)
10–19	756	717.9	1.05 (0.98–1.13)	143	118.6	1.21 (1.02–1.42)	128	148.1	0.86 (0.72–1.03)
≥ 20	712	663.4	1.07 (1.00–1.16)	134	113.9	1.18 (0.99–1.39)	175	146.5	1.19 (1.02–1.39)
Cystic tumors									
1–4	324	296.2	1.09 (0.98–1.22)	46	44.9	1.02 (0.75–1.37)	40	62.0	0.65 (0.46–0.88)
5–9	353	326.2	1.08 (0.97–1.20)	51	48.8	1.04 (0.78–1.37)	58	64.1	0.91 (0.69–1.17)
10–19	501	499.0	1.00 (0.92–1.10)	81	78.7	1.03 (0.82–1.28)	87	93.3	0.93 (0.75–1.15)
≥ 20	341	363.7	0.94 (0.84–1.04)	68	61.1	1.11 (0.86–1.41)	64	73.1	0.88 (0.67–1.12)
Age at first benign ovarian tumor (years)									
Solid tumors									
< 30	259	274.1	0.94 (0.83–1.07)	45	35.9	1.25 (0.91–1.68)	48	43.8	1.09 (0.81–1.45)
30–39	510	500.0	1.02 (0.93–1.11)	76	75.6	1.01 (0.79–1.26)	84	83.3	1.01 (0.80–1.25)
40–49	641	614.3	1.04 (0.96–1.13)	134	102.9	1.30 (1.09–1.54)	109	115.9	0.94 (0.77–1.13)
≥ 50	844	697.5	1.21 (1.13–1.29)	157	130.2	1.21 (1.02–1.41)	231	207.4	1.11 (0.97–1.27)
Cystic tumors									
< 30	184	193.9	0.95 (0.82–1.10)	23	23.7	0.97 (0.61–1.45)	30	32.6	0.92 (0.62–1.31)
30–39	386	393.7	0.98 (0.88–1.08)	59	56.9	1.04 (0.79–1.34)	53	66.3	0.80 (0.60–1.05)
40–49	485	485.8	1.00 (0.91–1.09)	78	77.9	1.00 (0.79–1.25)	82	87.0	0.94 (0.75–1.17)
≥ 50	464	411.7	1.13 (1.03–1.23)	86	75.1	1.15 (0.92–1.41)	84	106.5	0.79 (0.63–0.98)

First year of follow-up is excluded

and breast cancer [32, 33] which is largely in alignment with our results.

In our study, the increased risk of breast cancer in women with a first benign ovarian tumor diagnosed at age ≥ 50 years might be due to a high accumulated estrogen exposure throughout life. To our knowledge, the association between estrogen exposure and solid benign ovarian tumors is unknown, but one previous study suggested an association between high serum estradiol levels and ovarian cysts in premenopausal women [34]. Furthermore, the cumulative estrogen exposure on breast tissue is also believed to influence the risk of breast cancer [35]. Factors that are believed indirectly to be a measure of higher estrogen levels are early menarche and late menopause [35]. Unfortunately, we were not able to stratify on these variables in our study.

To our knowledge, no previous studies have investigated the association between benign ovarian tumors and different histologic subtypes of breast cancer. A review from 2015 reported a significantly stronger association between lobular breast cancer and age at menarche, age at menopause and age at first birth, compared with ductal breast cancer [6]. In our study, we did not see any marked difference between the risk of ductal and lobular breast cancer among women with benign ovarian tumors. However, it is important to note that the vast majority of all breast cancer cases are ductal adenocarcinomas [4, 6] and differences between the two subtypes may therefore be difficult to detect.

When assessing the association between benign ovarian tumors and breast cancer, it would have been interesting to look at differences according to estrogen-receptor (ER) and progesterone-receptor (PR) status. One of the previous studies investigating the risk of breast cancer in women with a benign ovarian cyst found decreased risk of overall breast cancer as well as in women with ER- and PR-positive breast cancer, whereas no association with

ER- and PR-negative breast cancer was observed [18]. Unfortunately, we were not able to investigate this association in our study.

In the present study, the histologic category "other types of breast cancer" is a mixed group of rare tumors. The association between benign ovarian tumors and these different histopathologic subtypes might therefore not be as straight forward as the other two types of breast cancer. This could explain why our results for this group are more inconsistent, showing decreased risk for women with a cystic ovarian tumor 1–4 years after diagnosis and for women aged ≥ 50 years at cystic tumor diagnosis.

To our knowledge, this is the largest cohort study examining the association between breast cancer and different histologic subtypes of benign ovarian tumors. We identified exposure and outcome through high-quality population-based registries in Denmark, and therefore, recall-bias was not an issue in our study. Furthermore, we were able to include both in- and outpatients, although information on outpatients is only available from 1995 and onwards in the Danish National Patient Register. Patients diagnosed with benign ovarian tumors at private gynecologists are, however, not included in the National Patient Register. Therefore, we cannot rule out that our risk estimates are slightly underestimated, and furthermore, if women who are hospitalized with a benign ovarian tumor differ markedly from those women treated at private gynecologists, our results may not be generalizable to the entire background population. Another limitation is that we were not able to adjust for potential confounding factors.

In conclusion, women with solid benign ovarian tumors are at increased risk of breast cancer. In particular, excess risks were seen up to 20 years or more after diagnosis and among women aged ≥ 50 years at the time of ovarian tumor diagnosis. The possible underlying mechanisms behind these associations must be investigated further. We did not find marked differences in risk estimates for ductal and lobular breast cancers.

Acknowledgement We wish to thank Lea Elsborg Hansen Olsen for help with data management.

Author contributions AJ and SKK initiated and designed the study. MG and KR performed the literature search. MG drafted the manuscript. All authors critically revised subsequent drafts. All authors read and approved the submitted version and take full responsibility for the content of the manuscript.

Funding No funding was obtained for this project.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent In Denmark, informed consent is not required for register-based studies.

References

1. Globocan database. http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf. Accessed 12 Dec 2018
2. Engholm G, Ferlay J, Christensen N, Hansen H L, Hertzum-Larsen R, Johannesen T B, et al NORDCAN: cancer incidence, mortality, prevalence and survival in the Nordic Countries, Version 8.1 (28.06.2018). Association of the Nordic Cancer Registries, Danish Cancer Society. http://www.ancr.nu. Accessed 12 Dec 2018
3. Jensen MB, Ejlertsen B, Mouridsen HT, Christiansen P, for the Danish Breast Cancer Cooperative Group (2016) Improvements in breast cancer survival between 1995 and 2012 in Denmark: the importance of earlier diagnosis and adjuvant treatment. Acta Oncol 55(Suppl 2):24–35
4. Anderson WF, Pfeiffer RM, Dores GM, Sherman ME (2006) Comparison of age distribution patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomark Prev 15(10):1899–1905
5. McPherson K, Steel CM, Dixon JM (2000) ABC of breast diseases: breast cancer—epidemiology, risk factors and genetics. BMJ 321(7261):624–628
6. Dossus L, Benusiglio PR (2015) Lobular breast cancer: incidence and genetic and non-genetic risk factors. Breast Cancer Res 17:37
7. McDonald JM, Modesitt SC (2006) The incidental postmenopausal adnexal mass. Clin Obstet Gynecol 49(3):506–516
8. Booth M, Beral V, Maconochie N, Carpenter L, Scott C (1992) A case-control study of benign ovarian tumours. J Epidemiol Community Health 46:528–531
9. Greenlee RT, Kessel B, Williams CR, Riley TL, Ragard LR, Hartge P et al (2010) Prevalence, incidence and natural history of simple ovarian cysts among women over age 55 in a large cancer screening trial. Am J Obstet Gynecol 202(4):373
10. Christensen JT, Boldsen JL, Westergaard JG (2002) Functional ovarian cysts in premenopausal and gynecologically healthy women. Contraception 66(3):153–157
11. Parazzini F, Moroni S, Negri E, Crosignani PG (1996) Risk factors for seromucinous benign ovarian cysts in northern Italy. J Epidemiol Community Health 51:449–452
12. Parazzini F, Moroni S, Negri E, La Vecchia C, Dal Pino D, Ricci E (1996) Risk factors for functional ovarian cysts. Epidemiology 7(5):547–549
13. Sharma A, Gentry-Maharaj A, Burnell M, Fourkala E, Campbell S, Amso N et al (2012) Assessing the malignant potential of ovarian inclusion cysts in postmenopausal women within the UK collaborative trial of ovarian cancer screening (UKCTOCS): a prospective cohort study. BJOG 119(2):207–219
14. Borgfeldt C, Andolf E (2004) Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. Acta Obstet Gynecol Scand 83:395–400
15. Franceschi S, La Vecchia C, Negri E, Parazzini F, Boyle P (1990) Breast cancer risk and history of selected medical conditions linked with female hormones. Eur J Cancer 26(7):781–785
16. Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton LA (1997) Breast cancer risk associated with gynecologic surgery and indications for such surgery. Int J Cancer 70:150–154

17. Moseson M, Koenig KL, Shore RE, Pasternack BS (1993) The influence of medical conditions associated with hormones on the risk of breast cancer. Int J Epidemiol 22(6):1000–1009
18. Knight JA, Lesosky M, Blackmore KM, Voigt LF, Holt VL, Bernstein L et al (2008) Ovarian cysts and breast cancer: results from the Women's Contraceptive and Reproductive Experiences Study. Breast Cancer Res Treat 109(1):157–164
19. Knight JA, John EM, Milne RL, Dite GS, Balbuena R, Shi EJ et al (2006) An inverse association between ovarian cysts and breast cancer in the Breast Cancer Family Registry. Int J Cancer 118(1):197–202
20. Bosetti C, Scotti L, Negri E, Talamini R, Levi F, Franceschi S et al (2006) Benign ovarian cysts and breast cancer risk. Int J Cancer 119(7):1679–1682
21. Talamini R, Franceschi S, Favero A, Negri E, La Vecchia C (1997) Selected medical conditions and risk of breast cancer. Br J Cancer 75(11):1699–1703
22. Jung SJ, Song M, Choi JY, Song N, Park SK, Yoo KY et al (2013) Association of selected medical conditions with breast cancer risk in Korea. J Prev Med Public Health 46(6):346–352
23. Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD et al (1999) Breast cancer risk in young women and history of selected medical conditions. Int J Epidemiol 28:816–823
24. Lynge E, Sandegaard JL, Rebolj M (2011) The Danish national patient register. Scand J Public Health 39(7 Suppl):30–33
25. Pedersen CB (2011) The Danish civil registration system. Scand J Public Health 39(7 Suppl):22–25
26. Gjerstorff ML (2011) The Danish cancer registry. Scand J Public Health 39(7 Suppl):42–45
27. Ressing M, Blettner M, Klug SJ (2010) Data analysis of epidemiological studies: part 11 of a series on evaluation of scientific publications. Dtsch Arztebl Int 107(11):187–192
28. Breslow NE, Day NE (1987) Rates and rate standardization. Statistical methods in cancer research—volume II: the design and analysis of cohort studies. IARC Scientific Publications No 82. International Agency for Research on Cancer, pp 48–79
29. Soegaard M, Kjaer SK, Cox M, Wozniak E, Hogdall E, Hogdall C et al (2008) BRCA1 and BRCA2 mutation prevalence and clinical characteristics of a population-based series of ovarian cancer cases from Denmark. Clin Cancer Res 14(12):3761–3767
30. Loman N, Johannsson O, Kristoffersson U, Olsson H, Borg A (2001) Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. J Natl Cancer Inst 93(16):1215–1223
31. Ehrmann DA (2005) Polycystic ovary syndrome. N Engl J Med 352:1223–1236
32. Barry JA, Azizia MM, Hardiman PJ (2014) Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 20(5):748–758
33. Gottschau M, Kjaer SK, Jensen A, Munk C, Mellemkjaer L (2015) Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study. Gynecol Oncol 136(1):99–103
34. Metindir J, Aslan S, Bilir G (2005) Ovarian cyst formation in patients using tamoxifen for breast cancer. Jpn J Clin Oncol 35(10):607–611
35. Clemons M, Goss P (2001) Estrogen and the risk of breast cancer. N Engl J Med 344(4):276–285