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Research Paper

Pregnancy Loss and Cancer Risk: A Nationwide Observational Study

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ABSTRACT

Background: Cancer is the second leading cause of death worldwide. Few studies have investigated if recurrent pregnancy loss is associated with an increased risk of cancer. We aimed to assess whether pregnancy loss is associated with later cancer development.

Methods: We identified all invasive cancers after age 40, among all Danish women born between January 1957 and December 1972, ensuring a full reproductive history. Cases were matched by birth year 1:10 to cancer-free controls. Women were followed until the end of 2017. The number of pregnancy losses (miscarriages or still births) was correlated to long-term cancer risk using conditional logistic regression, providing odds ratios for specific cancers with different numbers of pregnancy losses, all adjusted for age, education, and other potential confounders.

Findings: The study included 28,785 women with cancer (mean age 48.7 [SD 5.0]) and 283,294 matched controls (mean age 48.6 [SD 5.0]). We found no overall association between pregnancy loss and later development of 11 site-specific types of cancer or cancer overall. Taking the sequence of pregnancy losses into account, primary recurrent pregnancy loss (three consecutive pregnancy losses without prior live birth) was associated with later overall cancer by an odds ratio of 1.27 (1.04–1.56). Secondary recurrent pregnancy loss showed no association to cancer.

Interpretation: Pregnancy loss was not associated with later cancer development. Women with primary recurrent pregnancy loss had a borderline significant association to later cancer overall, this may be a chance finding.

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Research in Context

Evidence Before This Study

We searched PubMed for relevant studies published before Feb 1, 2019 for associations between pregnancy loss and cancer. The following search phrases were used: "pregnancy loss", "abortion", or "miscarriage"; and "cancer". Articles were critically assessed for relevance by the first author. No languages were excluded from our search.

The association between pregnancy loss and breast cancer has been summarized in two meta-analyses including 59 studies; they found no positive correlation. Two contradicting studies investigated the outcome of ovarian cancer, one found an increased risk while the other did not. However, out of these 61 studies none reported the effect of recurrent pregnancy loss, 49 relied on self-reported data, and most did not report the number of pregnancy losses hiding a potential dose–response relationship. One study investigating the influence of recurrent pregnancy loss (RPL) on the risk of later cancer development, found an increased risk of breast cancer and cancer overall as compared to women without RPL.

RPL is of specific interest as the frequency of euploid losses increases, with increasing number of pregnancy losses,

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pointing to non-fetal causes. Furthermore, women with RPL have been found to have an increased risk of myocardial infarction and stroke later in life.

Added Value of This Study

This study is the first to examine both the number of pregnancy losses, and the influence of consecutive or non-consecutive pregnancy loss patterns, on the risk of 11 site-specific types of cancer and on cancer overall. Our study finds no strong association between pregnancy loss and later cancer development, thereby contradicting the study which found RPL to be a risk factor for later cancer.

Implications of All the Available Evidence

Pregnancy loss is not associated with an increased risk of cancer later in life, taking this potential burden from women already struggling to achieve a live birth.

1. Introduction

Reproductive factors have repeatedly been associated with different cancers. Young age at first full-term pregnancy lowers the long-term risk of breast cancer [1,2], however, postpartum the short-term risk of breast cancer is increased [3]. Each childbirth reduces the risk of ovarian and endometrial cancer. As cancer is a major contributor to morbidity and mortality worldwide, identifying groups at risk is essential for early detection of disease.

Pregnancy loss is the most common serious complication in early pregnancy, and at least one in three pregnancies end in a loss [4]. Pregnancy loss has been positively correlated to future risk of myocardial infarction, cerebral infarction [5,6], hypertension, type 2 diabetes, and hypercholesterolemia [7], although the etiology and significance are largely unknown.

Most studies have focused on pregnancy loss as a dichotomous exposure (ever/never) and later risk of breast cancer, and ovarian cancer. Results from most of these studies indicate no association [8–10], although some find a positive correlation [11,12].

Recurrent pregnancy loss is most often defined as three consecutive pregnancy losses and affects 1–2% of women trying to conceive [13], and of those referred to a tertiary center, two thirds have at least one live birth within five years [14]. Few studies have examined consecutive pregnancy losses as a possible risk indicator for later cancer. A recent study found two consecutive pregnancy losses to be positively associated with future breast and cervical cancer [15].

The aim of this study was to investigate if pregnancy loss is associated with cancer. Immunological mechanisms are known to play a role in specific types and successions of pregnancy loss [16–20], as well as in preventing different types of cancer [21]. Therefore, we examined exposure to these subtypes of pregnancy loss and their correlation to subsequent cancer development.

2. Methods

2.1. Sources of Data

Denmark has a free and universal public healthcare system. Since the founding of the Danish Civil Registration System in 1968, all individuals living in Denmark have been registered in this database with their permanent 10-digit personal identification number, marital status, vital status, kinship information, and past and present addresses. The personal identification number is used for contacts with essentially any Danish government agency, including hospital visits and purchase of prescription medicine. Supplementary Table S1 describes the registries used in this study; Supplementary Table S1 shows all the codes we searched for in these registries to define baseline characteristics, exposures and outcomes. Discharge diagnoses were coded using the International Classification of Diseases 8th revision before 1994, thereafter the 10th revision. Prescription medicine was coded using the Anatomical Therapeutic Chemical Classification System.

The Danish Health Registry, established in 1976, and the Danish Medical Birth Registry, established in 1973, provided registry-based follow-up of exposures and covariates for all Danish women. Cancer events (cases) were primarily identified in the Danish Cancer Registry, with virtually complete data on cancer diagnoses from 1987 throughout 2016, verified with pathology testing [22]. For 2017, data on cancer outcomes was provided by the Danish Health Registry, as data from 2017 was not yet available in the Danish Cancer Registry at the time of data extraction. All diagnoses and surgical codes were made by clinicians; pre-pregnancy weight and smoking status were self-reported. The gestational week of miscarriages has been registered since 1995.

2.2. Design

A nationwide cohort study with a case–control analysis.

2.3. Study Population

To ensure a full reproductive history, we included women born between January 1st, 1957 and December 31st, 1972 as they were between 5 and 20 years old when a full registry-based follow-up was possible from 1977. Supplementary Fig. S1 provides a Lexis diagram illustrating the selection of the study population.

Cases were women with a first-time invasive cancer, subdivided by site-specific cancer type: (i) breast, (ii) ovarian, (iii) endometrial, (iv) cervical, (v) bladder, (vi) renal, (vii) lung, (viii) gastrointestinal, (ix) brain, (x) hematological, (xi) melanoma, and (xii) all-type cancer, except non-melanoma skin cancer. To evaluate the effect of events occurring throughout the reproductive age on later risk of cancer, we excluded women with first-time cancer before 40 years of age. The earliest calendar year an outcome of interest could occur was therefore 1997, while the latest was 2017. Controls were sampled at random from all Danish female residents, using the Danish Civil Registration System, matching each case by birth year to 10 controls alive at the event date, using exact matching. The index date for cases was the date of cancer diagnosis, while for controls the index date was the date of cancer for the case they were specifically matched to. Both cases and controls were excluded if they resided outside of Denmark for over six months between their 20th birthday and the index date, as they potentially could have had unregistered pregnancies or cancers abroad.

2.4. Exposures

The primary exposure of interest was one or more pregnancy losses, defined as either a miscarriage or a still birth. Miscarriages were identified in the Danish Health Registry and stillbirths were identified in the Danish Medical Birth Registry. Women *ever-pregnant* (i.e. one or more registered miscarriage, termination of pregnancy, still birth or live birth) were at the index date stratified to one of the following exposure groups: 0 pregnancy losses, one pregnancy loss, two pregnancy losses or, three or more pregnancy losses. In addition to the number of pregnancy losses, we also examined specific a priori defined subtypes of pregnancy loss, known or hypothesized to be associated with immunological disturbances: (i) Three pregnancy losses before 30 years of age, (ii)

Three consecutive pregnancy losses, (iii) Primary recurrent pregnancy loss (three consecutive pregnancy losses not preceded by a live birth), (iv) Secondary recurrent pregnancy loss (three consecutive pregnancy losses preceded by a live birth), (v) Three consecutive pregnancy losses preceded by a pregnancy complicated by either preterm birth, intrauterine growth restriction, preeclampsia or placental abruption, (vi) Two second trimester pregnancy losses, and (vii) A still birth. Besides three consecutive registered pregnancy losses, a diagnosis of recurrent pregnancy loss was also considered as three consecutive pregnancy losses. Finally, we investigated the impact of *never-pregnant* (i.e. no registered miscarriage, termination of pregnancy, still birth or live birth) on cancer risk, with *ever-pregnant* as reference group.

2.5. Confounders

We considered baseline characteristics seen in Table 1. Data was provided using the aforementioned registries, in addition to the Danish Registry of Medicinal Product Statistics (the Prescription Registry). We adjusted for the following potential confounders in all adjusted analyses: attained age at index date (continuous variable) and educational level of a bachelor's degree or higher (binary variable). Breast cancer was further adjusted for parity (indicator variable), age under 30 at first live birth (binary variable), and ever/never use of systemic hormonal contraception (binary variable). Ovarian cancer was adjusted for parity and ever/never use of systemic hormonal contraception. Endometrial cancer was adjusted for parity, ever/never use of systemic hormonal contraception, and diabetes (binary variable). Diabetes and use of systemic hormonal contraception were identified by drug purchases in the Prescription Registry, available from 1995 to 2014 at the time of data extraction. Pre-pregnancy smoking habits and pre-pregnancy body mass index were registered in the Danish Medical Birth Registry from year 1991 to 2004, respectively, thus resulting in missing values for women with only live births before these dates or women with no live births. A sensitivity analysis further adjusting for ever/never smoking (binary variable) was calculated for the lung cancer outcome for those with this data available. Likewise, a sensitivity analysis further adjusting for ever/never body mass index >30 (binary variable) was calculated for the outcome of gastro-intestinal cancer.

2.6. Statistical Analyses

Numerical baseline characteristics were described by a mean and standard deviation, and differences between case and control groups were tested using the Mann–Whitney *U* test. Binary variables were described by proportions, and differences between cases and controls were calculated using Pearson's χ^2-test. A *p*-value <0.05 was considered statistically significant. The measure of association between exposure and outcome variables was an odds ratio, calculated using conditional logistic regression. Results were presented with 95% confidence intervals. Programming and statistical analyses were performed in SAS software version 9.4 (SAS Institute), Stata software version 15 (StataCorp LLC) and R version 3.5 (The R Foundation for Statistical Computing).

The Danish Health Data Authority approved access to registry data. No ethical approval was required.

3. Results

The study included 28,785 women with incident invasive cancer and 283,294 matched cancer-free controls (Fig. 1). The overall mean age was 48.6 years at the index date (standard deviation 5.0 years). The most common site-specific cancers were breast cancer (42.3%), melanoma (11.6%), and gastro-intestinal cancer (11.0%).

Although most differences between cases and controls were minor, some were notable (Table 1): Educational level was lower among all cancer groups, except for the melanoma group. Comparing cases to controls: fewer women with breast cancer had given birth before age 30, fewer women with gynecological cancers had ever used systemic hormonal contraception, more women with endometrial cancer and renal cancer had diabetes, and previous induced abortion was more prevalent in the cervical cancer group.

Among *ever-pregnant* women with 0 pregnancy losses as reference group, we generally found no correlation between the number of pregnancy losses and later cancer risk (Table 2). Adjusting for potential confounders only changed our estimates marginally. Endometrial cancer showed a non-significant inverse association with three or more pregnancy losses, correlated by an adjusted odds ratio of 0.75 (0.34–1.66). Likewise, melanoma displayed an inverse association, however, only two pregnancy losses and not three or more was significantly associated with a decreased melanoma risk, adjusted odds ratio 0.72 (0.57–0.90) and 0.69 (0.47–1.01), respectively. Renal cancer and hematological cancer displayed a positive non-significant association with pregnancy loss, with exposure to three or more pregnancy losses correlated to renal cancer by an adjusted odds ratio of 1.97 (0.90–4.28) and to hematological cancer by an adjusted odds ratio of 1.43 (0.90–2.25).

For the different subtypes of pregnancy loss among *ever-pregnant* women (Table 3) we found few significant associations: the exposure to three pregnancy losses before age 30 was positively correlated to later lung cancer; adjusted odds ratio 2.22 (1.28–3.86). In a sensitivity analysis further adjusting for tobacco smoking, the association was weakened and no longer significant (Supplementary Table S3). Two second trimester pregnancy losses conferred an adjusted odds ratio of 4.00 (1.38–11.60) for hematological cancers. Women with recurrent pregnancy loss had an adjusted odds ratio for gastro-intestinal cancer of 1.37 (0.91–2.07) and of 1.15 (0.99–1.32) for all cancers (Fig. 2). Stratifying this exposure into primary or secondary recurrent pregnancy loss, only primary recurrent pregnancy loss was associated with the two cancer groups; odds ratios 2.00 (1.16–3.45) and 1.27 (1.04–1.56), respectively. Similarly, exposure to three pregnancy losses before age 30 was associated with gastro-intestinal cancer; adjusted odds ratio 1.86 (1.11–3.11).

In Supplementary Table S4 we focused on the exposure to recurrent pregnancy loss and subdivided our population according to the age at cancer diagnosis, over or under 50 years of age. We found that exposure to recurrent pregnancy loss confers a statistically significant increased odds ratio of gastro-intestinal cancer (adjusted odds ratio 1.92 [1.11–3.26]), hematological cancer (odds ratio 1.97 [1.02–3.80]) and cancer overall (adjusted odds ratio 1.20 [1.01–1.44]), between ages 40 and 49, but not in the age group 50–61. In contrast, exposure to recurrent pregnancy loss had a tendency towards an increased odds ratio of gynecological cancers in the age group 50–61 compared to the younger age group, however, this was not statistically significant.

Never being pregnant was positively associated with later ovarian cancer; adjusted odds ratio 1.72 (1.43–2.06), endometrial cancer; 2.92 (2.49–3.43) and inversely associated with melanoma and breast cancer; adjusted odds ratio 0.88 (0.78–0.99) and 0.94 (0.88–1.00), respectively (Supplementary Table S5).

In the analysis for gastro-intestinal cancer and cancer overall, we further adjusted for body mass index ≥ 30 in the subgroup of patients with weight data available (6.0%). This had very little effect on the results (Supplementary Table S6).

Table 1
Characteristics of cancer cases and controls at the index date according to cancer type.

	Cases	Controls	Cases	Controls	Cases	Controls
	Breast cancer		**Ovarian cancer**		**Endometrial cancer**	
n	12,181	120,136	901	8857	982	9598
Mean age (SD) - yr	48.4 (4.7)	48.5 (4.7)	48.5 (4.7)	48.4 (4.7)	48.5 (5.0)	48.5 (5.0)
Parity (SD)	1.8 (1.0)	1.9 (1.1)	1.6 (1.1)	1.9 (1.1)*	1.4 (1.1)	1.9 (1.1)*
Age under 30 at first live birth - %	64.4	67.7*	62.2	68.1*	56.0	68.6*
Previous induced abortion - %	28.3	28.6	27.0	28.5	19.8	28.1*
Diabetes Mellitus - %	2.5	3.2*	4.3	3.2	10.0	3.2*
Asthma - %	2.6	2.9	3.2	2.7	2.6	2.8
Inflammatory bowel disease - %	1.4	1.4	2.0	1.3	1.4	1.7
Systemic hormonal contraception, ever use - %	54.9	52.5*	40.2	50.0*	35.6	48.7*
Educational level of bachelor's degree or higher - %	29.0	29.4	20.5	29.4*	27.1	29.0
Body-Mass Index ≥30 - %[a]	8.2	13.6*	13.9	14.3	17.7	13.5
Smoking - %[b]	31.8	31.1	35.1	31.1	24.4	30.6
	Cervical cancer		**Bladder cancer**		**Renal cancer**	
n	1282	12,670	183	1780	393	3860
Mean age (SD) - yr	45.6 (4.6)	45.5 (4.6)	50.2 (4.9)	49.9 (4.8)	49.9 (5.0)	49.8 (5.0)
Parity (SD)	1.8 (1.2)	1.9 (1.1)*	1.7 (1.2)	1.9 (1.1)*	2.0 (1.1)	1.9 (1.1)
Age under 30 at first live birth - %	66.0	67.1	67.8	68.5	74.3	68.1
Previous induced abortion - %	32.6	28.8*	32.8	27.8	30.3	28.9
Diabetes Mellitus - %	2.4	3.1	4.4	3.5	9.4	3.0*
Asthma - %	1.5	2.5*	3.3	2.9	3.6	2.9
Inflammatory bowel disease - %	2.1	1.4*	<5	1.4	2.8	1.3*
Systemic hormonal contraception, ever use - %	55.9	56.5	52.5	50.3	51.2	51.8
Educational level of bachelor's degree or higher - %	21.5	30.5*	13.7	28.0*	17.1	30.3*
Body-Mass Index ≥30 - %[a]	16.1	13.2	<5	9.8	37.5	15.4*
Smoking - %[b]	41.5	30.5*	54.2	30.5*	49.2	29.8*
	Lung cancer		**Gastro-intestinal cancer**		**Brain cancer**	
n	2095	20,533	3154	30,834	398	3890
Mean age (SD) - yr	50.7 (4.8)	50.6 (4.8)	50.0 (5.0)	50.0 (5.0)	48.2 (5.3)	48.1 (5.4)
Parity (SD)	1.8 (1.1)	1.8 (1.1)*	1.8 (1.1)	1.9 (1.1)*	1.9 (1.1)	1.8 (1.1)
Age under 30 at first live birth - %	72.0	68.7*	66.4	68.1	68.6	67.6
Previous induced abortion - %	34.3	28.3*	29.4	28.5	28.4	28.6
Diabetes Mellitus - %	4.7	3.4*	6.0	3.3*	2.0	3.1
Asthma - %	4.8	2.9*	2.9	2.9	5.0	2.7*
Inflammatory bowel disease - %	1.6	1.3	2.2	1.4*	2.3	1.5
Systemic hormonal contraception, ever use - %	50.1	47.0*	49.0	49.9	56.5	51.8
Educational level of bachelor's degree or higher - %	5.8	28.1*	16.5	29.2*	12.1	28.4*
Body-Mass Index ≥30 - %[a]	14.3	12.5	19.4	12.9*	8.3	10.7
Smoking - %[b]	79.2	31.4*	39.1	31.0*	37.3	31.1
	Hematological cancer		**Melanoma**		**All cancers[c]**	
n	1341	13,250	3339	32,974	28,785	283,294
Mean age (SD) - yr	49.3 (5.2)	49.2 (5.2)	47.4 (4.8)	47.3 (4.8)	48.7 (5.0)	48.6 (5.0)*
Parity (SD)	1.8 (1.1)	1.9 (1.1)*	1.8 (1.0)	1.9 (1.1)	1.8 (1.1)	1.9 (1.1)*
Age under 30 at first live birth - %	65.8	67.4	65.5	67.2*	65.5	67.8*
Previous induced abortion - %	30.8	28.3	26.7	28.2	28.8	28.4
Diabetes Mellitus - %	4.3	3.2	2.8	3.0	3.8	3.2*
Asthma - %	3.4	3.1	2.5	2.9	2.9	2.9
Inflammatory bowel disease - %	1.9	1.3	1.7	1.4	1.7	1.4*
Systemic hormonal contraception, ever use - %	50.5	51.8	59.7	57.0*	24.1	29.4*
Educational level of bachelor's degree or higher - %	23.6	29.7*	32.6	30.0*	24.1	29.1*
Body-Mass Index ≥30 - %[a]	11.1	12.3	7.6	12.9*	11.1	13.4*
Smoking - %[b]	35.4	30.9*	25.6	31.2*	35.8	31.1*

(Notice the number of cases and controls in 'All cancers' is greater than the subgroups combined as other types of cancer were included.)
SD: Standard Deviation.
<5: Data not available for presentation due to less than five observations.
* Indicates a p-value of <0.05 between the case and control group.
[a] Information only available for 6.0% of all patients.
[b] Information only available for 53.5% of all patients.
[c] All types of cancer, except non-melanoma skin cancer.

4. Discussion

In this nationwide observational study of 28,785 women with incident invasive cancer and a full registry-based reproductive history, we found no evidence of an overall association between number of pregnancy losses and later cancer development. Among those exposed to subtypes of pregnancy loss correlated to immunological mechanisms, we found sporadic associations to later cancer, however, we found no clear trend indicating a robust positive association to site-specific cancers or cancer in general.

4.1. Pregnancy Loss and Cancer Risk

Two meta-analyses on the association between pregnancy loss and breast cancer have been published. The first by *the Collaborative Group on Hormonal Factors in Breast Cancer* published in

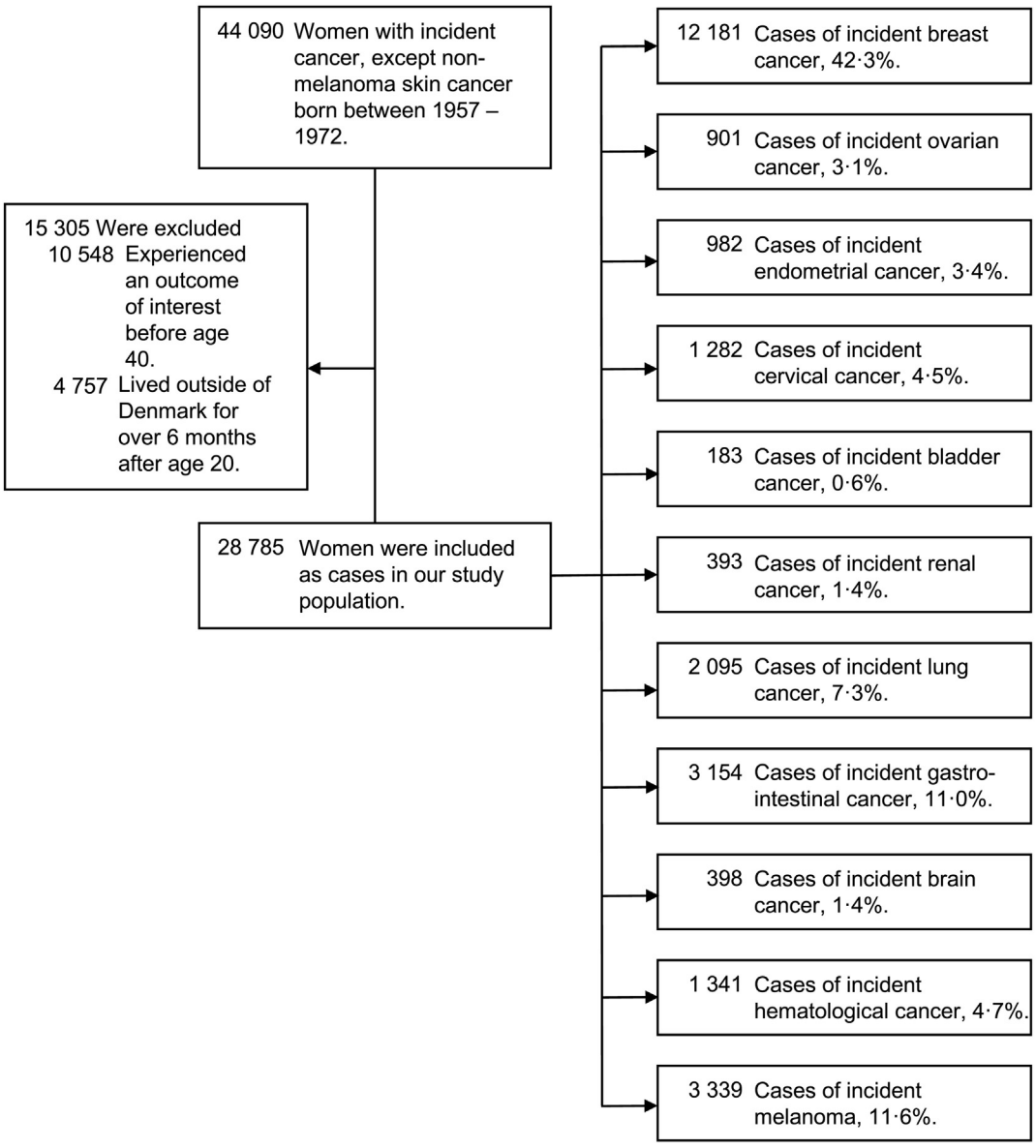

Fig. 1. Flow chart showing the selection of cases for the study. The sum of the subtypes of cancers does not add up to the total case population as 8.7% develop other types of cancer.

2004 [8], included 52 studies. Of these, 12 studies recorded pregnancy loss in a prospective manner (i.e. before the cancer diagnosis). Among the prospective studies, eight studies relied on self-reported data. Only two prospective studies relying on hospital records, reported the number of pregnancy losses more specifically than ever/never, these evaluated 482 cancer cases [23,24]. The second meta-analysis by Guo et al. included no new studies with non-self-reported data on pregnancy loss [9]. None of the included studies evaluated the effect of consecutive losses. Both meta-analyses found no association between pregnancy loss and breast cancer, which is in accordance with our findings.

To our knowledge, the only other study investigating recurrent pregnancy loss and subsequent risk of cancer is the study by Charach et al. [15]. They found a significantly increased risk of cervical cancer (odds ratio 1.6, *p*-value 0.038), breast cancer (odds ratio 1.7, *p*-value 0.001), and female malignancy overall with an adjusted hazard ratio of 1.35 (95% confidence interval 1.1–1.6). The study included cases at their first pregnancy after a recurrent pregnancy loss defined as two or more consecutive pregnancy losses, while controls were included at a random pregnancy. Cases were therefore on average 2.52 years older, *p*-value <0.001 and this age difference was apparently not adjusted for in the analyses.

4.2. Special Pregnancy Loss Groups

Among pregnancy losses in the first trimester, 50–70% have been found to have fetal chromosomal abnormalities [25,26]. With multiple first trimester pregnancy losses the proportion of euploid losses increases [27]. The underlying pathophysiology behind the euploid pregnancy losses is largely unknown. Some may be due to genetic errors of the fetus such as microdeletions, point mutations, epigenetic changes, and structural abnormalities, while others may be caused by maternal factors, including uterine, coagulative, endocrine, and immunological disturbances [16–20].

Known risk factors for pregnancy loss and recurrent pregnancy loss include: increasing maternal age, previous pregnancy loss, parental genetic abnormalities, polycystic ovarian syndrome, coagulative disorders, endocrine diseases such as thyroid disease and

Table 2
Association between number of pregnancy losses and cancer in ever-pregnant women.

	Cases	Controls	OR	OR^{adj} (95%CI)	Cases	Controls	OR	OR^{adj} (95%CI)
	Breast cancer				**Ovarian cancer**			
n	10,918	107,009			736	7847		
0 PL	8411 (77.0)	82,045 (76.7)	1	1	581 (78.9)	6098 (77.7)	1	1
1 PL	1926 (17.6)	19,362 (18.1)	0.97	0.98 (0.93–1.04)	113 (15.4)	1360 (17.3)	0.86	0.86 (0.69–1.07)
2 PL	424 (3.4)	4046 (3.4)	1.01	0.99 (0.89–1.10)	32 (4.4)	292 (3.7)	1.11	1.18 (0.80–1.72)
≥3 PL	157 (1.4)	1556 (1.5)	0.97	0.97 (0.81–1.16)	10 (1.4)	97 (1.2)	1.06	1.11 (0.56–2.17)
	Endometrial cancer				**Cervical cancer**			
n	734	8608			1123	11,270		
0 PL	580 (79.0)	6588 (76.5)	1	1	878 (78.2)	8616 (76.5))	1	1
1 PL	125 (17.0)	1570 (18.2)	0.92	0.93 (0.76–1.15)	195 (17.4)	2045 (18.2)	0.94	0.95 (0.80–1.11)
2 PL	22 (3.0)	333 (3.9)	0.70	0.69 (0.44–1.09)	35 (3.1)	435 (3.0)	0.77	0.78 (0.55–1.12)
≥3 PL	7 (1.0)	117 (1.4)	0.78	0.75 (0.34–1.66)	15 (1.3)	174 (1.5)	0.88	0.90 (0.53–1.54)
	Bladder cancer				**Renal cancer**			
n	~155	1585			360	3453		
0 PL	124 (79.5)	1200 (75.7)	1	1	257 (71.4)	2662 (77.1)	1	1
1 PL	24 (15.4)	299 (18.9)	0.80	0.83 (0.52–1.32)	76 (21.1)	614 (17.8)	1.27	1.31 (0.99–1.73)
2 PL	7 (4.5)	70 (4.4)	1.08	1.24 (0.54–2.81)	19 (5.3)	138 (4.0)	1.37	1.39 (0.83–2.34)
≥3 PL	<5	16 (1.0)	n/a	n/a	8 (2.2)	39 (1.1)	1.94	1.97 (0.90–4.28)
	Lung cancer				**Gastro–intestinal cancer**			
n	1857	18,244			2774	27,421		
0 PL	1424 (76.7)	13,951 (76.5)	1	1	2149 (77.5)	21,009 (76.6)	1	1
1 PL	341 (18.4)	3303 (18.1)	1.03	1.08 (0.95–1.23)	482 (17.4)	4981 (18.2)	0.93	0.95 (0.85–1.05)
2 PL	64 (3.5)	717 (3.9)	0.86	0.91 (0.69–1.19)	105 (3.8)	1075 (3.9)	0.95	0.98 (0.79–1.20)
≥3 PL	28 (1.5)	273 (1.5)	1.04	1.03 (0.69–1.54)	38 (1.4)	356 (1.3)	1.06	1.08 (0.76–1.53)
	Brain cancer				**Haematological cancer**			
n	359	3452			1182	11,787		
0 PL	280 (78.0)	2685 (77.8)	1	1	898 (76.0)	9020 (76.5)	1	1
1 PL	58 (16.2)	583 (16.9)	0.94	0.93 (0.69–1.26)	213 (18.0)	2145 (18.2)	1.01	1.01 (0.86–1.19)
2 PL	12 (3.3)	141 (4.1)	0.83	0.81 (0.44–1.50)	49 (4.2)	465 (4.0)	1.07	1.06 (0.78–1.44)
≥3 PL	9 (2.5)	43 (1.3)	**2.09**	1.96 (0.93–4.12)	22 (1.9)	157 (1.3)	1.43	1.43 (0.90–2.25)
	Melanoma				**All cancers**[a]			
n	2360	22,477			25,420	252,218		
0 PL	2360 (78.3)	22,477 (76.6)	1	1	19,591 (77.1)	193,340 (76.7)	1	1
1 PL	538 (17.8)	5308 (18.1)	0.96	0.96 (0.87–1.06)	4506 (17.7)	45,660 (18.1)	0.98	0.98 (0.95–1.02)
2 PL	87 (2.9)	1149 (3.9)	**0.72**	**0.72 (0.57–0.90)**	963 (3.8)	9671 (3.8)	0.98	0.98 (0.92–1.05)
≥3 PL	30 (1.0)	411 (1.4)	0.70	0.69 (0.47–1.01)	359 (1.4)	3547 (1.4)	1.01	1.02 (0.91–1.14)

Bold font signifies a statistically significant result with regard to the 95% confidence interval (CI).
OR: Crude odds Ratio, confidence interval not shown due to size of table. OR^{adj}: Odds Ratio, adjusted for age and attainment of bachelor's degree. Breast cancer additionally adjusted for parity, age at first live birth and hormonal contraception ever/never use. Ovarian cancer additionally adjusted for parity and hormonal contraception ever/never use. Endometrial cancer adjusted for parity, hormonal contraception ever/never use, and diabetes.
<5: Data not available for presentation due to less than five observations, estimate therefore not available (n/a), and total n rounded to nearest 5.
[a] All invasive cancers, except non-melanoma skin cancer. PL: Pregnancy loss (miscarriage or still birth).

diabetes. More euploid losses are seen with high body mass index [28]. Life style factors such as alcohol consumption and smoking, appear to increase the risk of pregnancy loss in a dose–response manner [29]. However, the prognostic significance of the majority of hitherto identified risk factors remains largely unknown, and the chance of subsequent live birth is still based on maternal age and number of prior pregnancy losses [30].

We investigated specific a priori defined exposure subgroups previously shown to be correlated to immunological mechanisms and have a high risk of euploid loses (Table 3). Exposure to primary recurrent pregnancy loss showed the strongest association to cancer, driven primarily by an increased risk of gastro-intestinal cancer and hematological cancer. In the main analysis this was only significantly associated with the overall cancer, however, in a sensitivity analysis further stratifying according to age at cancer (Supplementary Table S4), the odds of these cancers was almost doubled at ages 40–49 years. The specific reasons for the modest increase in cancer risk among the primary recurrent pregnancy loss group, cannot be explained by the current study, however, our hypotheses include: A common precursor (e.g. a gene or environmental factor) increasing a woman's risk of both recurrent pregnancy loss and cancer. Another possibility is that exposure to recurrent pregnancy loss increases the risk of later cancer, by a mediating factor such as changes in life style or possibly by disturbing the maternal immune system, and crucially the ability to recognize precursors to cancer. However, we cannot rule out that the result arose from a chance finding, due to the nature of a 95% confidence interval, therefore reproducing our results in other populations is warranted.

Other statistically significant results were seen, e.g. three or more pregnancy losses before age 30 was associated with gastro-intestinal cancer and two pregnancy losses in the second trimester was positively associated with hematological cancer.

4.3. Never-pregnant

The group of women with no registered pregnancies likely comprises a heterogenic group, with two very different subgroups; the

Table 3
Association between subtypes of pregnancy loss and cancer in ever-pregnant women.

	Cases	Controls	OR^{adj} (95% CI)	Cases	Controls	OR^{adj} (95% CI)
	Breast cancer			**Ovarian cancer**		
n	10,918	107,009		736	7847	
RPL	105 (1.0)	889 (0.8)	1.10 (0.88–1.37)	8 (1.1)	55 (0.7)	1.62 (0.75–3.48)
Primary RPL	54 (0.5)	379 (0.4)	1.01 (0.96–1.07)	<5	19 (0.2)	n/a
Secondary RPL	51 (0.5)	510 (0.5)	0.98 (0.73–1.32))	<5	36 (0.5)	n/a
RPL after a complicated delivery[b]	10 (0.1)	61 (0.1)	1.86 (0.94–3.70)	<5	10 (0.1)	n/a
≥3 PL before age 30	42 (0.4)	427 (0.4)	1.04 (0.75–1.45)	<5	31 (0.4)	n/a
≥2 PL in 2nd. trimester	14 (0.1)	134 (0.1)	0.99 (0.54–1.80)	<5	9 (0.1)	n/a
≥1 still birth	79 (0.7)	1010 (0.9)	0.84 (0.66–1.07)	9 (1.2)	82 (1.0)	1.27 (0.60–2.69)
	Endometrial cancer			**Cervical cancer**		
n	734	8608		1123	11,270	
RPL	6 (0.8)	67 (0.8)	1.25 (0.52–3.01)	9 (0.8)	100 (0.9)	1.01 (0.51–2.02)
Primary RPL	<5	26 (0.3)	n/a	<5	54 (0.5)	<5
Secondary RPL	<5	41 (0.5)	n/a	7 (0.6)	46 (0.4)	1.67 (0.74–3.75)
RPL after a complicated delivery[b]	<5	5 (0.1)	n/a	<5	6 (0.1)	<5
≥3 PL before age 30	<5	26 (0.3)	n/a	6 (0.5)	64 (0.6)	0.92 (0.39–2.15)
≥2 PL in 2nd. trimester	<5	9 (0.1)	n/a	<5	19 (0.2)	<5
≥1 still birth	7 (1.0)	89 (1.0)	1.03 (0.43–2.45)	16 (1.4)	121 (1.1)	1.26 (0.74–2.14)
	Bladder cancer			**Renal cancer**		
n	156	1585		360	3453	
RPL	<5	11 (0.7)	n/a	<5	14 (0.4)	n/a
Primary RPL	<5	6 (0.4)	n/a	<5	9 (0.3)	n/a
Secondary RPL	<5	5 (0.3)	n/a	<5	5 (0.1)	n/a
RPL after a complicated delivery[b]	<5	<5	n/a	<5	<5	n/a
≥3 PL before age 30	<5	<5	n/a	<5	10 (0.3)	n/a
≥2 PL in 2nd trimester	<5	<5	n/a	<5	<5	n/a
≥1 still birth	<5	14 (0.9)	n/a	5 (1.4)	37 (1.1)	1.32 (0.51–3.41)
	Lung cancer			**Gastro–intestinal cancer**		
n	1857	18,244		2774	27,421	
RPL	12 (0.7)	145 (0.8)	0.88 (0.48–1.62)	28 (1.0)	207 (0.8)	1.37 (0.91–2.07)
Primary RPL	6 (0.3)	61 (0.3)	1.26 (0.53–3.01)	16 (0.6)	88 (0.3)	**2.00 (1.16–3.45)**
Secondary RPL	6 (0.3)	84 (0.5)	0.68 (0.30–1.58)	12 (0.4)	119 (0.4)	0.94 (0.50–1.76)
RPL after a complicated delivery[b]	<5	8 (0.04)	n/a	<5	14 (0.1)	n/a
≥3 PL before age 30	17 (0.9)	77 (0.4)	**2.22 (1.28–3.86)**	19 (0.7)	99 (0.4)	**1.86 (1.11–3.11)**
≥2 PL in 2nd trimester	<5	15 (0.1)	n/a	<5	22 (0.1)	n/a
≥1 still birth	25 (1.4)	176 (1.0)	1.32 (0.86–2.04)	28 (1.0)	256 (1.0)	1.13 (0.76–1.68)
	Brain cancer			**Haematological cancer**		
n	359	3452		1182	11,787	
RPL	<5	26 (0.8)	n/a	14 (1.2)	91 (0.8)	1.58 (0.89–2.80)
Primary RPL	<5	14 (0.4)	n/a	7 (0.6)	46 (0.4)	1.62 (0.73–3.65)
Secondary RPL	<5	12 (0.4)	n/a	7 (0.6)	45 (0.4)	1.51 (0.68–3.39)
RPL after a complicated delivery[b]	<5	<5	n/a	<5	5 (0.04)	n/a
≥3 PL before age 30	<5	8 (0.2)	n/a	7 (0.6)	52 (0.4)	1.38 (0.62–3.08)
≥2 PL in 2nd trimester	<5	<5	n/a	5 (0.4)	13 (0.1)	**4.00 (1.38–11.60)**
≥1 still birth	<5	27 (0.8)	n/a	7 (0.6)	109 (0.9)	0.63 (0.29–1.36)
	Melanoma			**All cancers**[a]		
n	2360	22,477		25,420	252,218	
RPL	18 (0.6)	235 (0.8)	0.75 (0.46–1.21)	229 (0.9)	2028 (0.8)	1.15 (0.99–1.32)
Primary RPL	11 (0.4)	108 (0.4)	0.98 (0.52–1.83)	111 (0.4)	898 (0.4)	**1.27 (1.04–1.56)**
Secondary RPL	7 (0.2)	127 (0.4)	0.55 (0.26–1.18)	118 (0.5)	1130 (0.5)	1.05 (0.86–1.27)
RPL after a complicated delivery[b]	<5	15 (0.1)	n/a	20 (0.1)	138 (0.1)	1.46 (0.89–2.37)
≥3 PL before age 30	7 (0.2)	107 (0.4)	0.64 (0.29–1.38)	113 (0.4)	997 (0.4)	1.12 (0.92–1.37)
≥2 PL in 2nd trimester	<5	36 (0.1)	n/a	33 (0.1)	280 (0.1)	1.18 (0.82–1.70)
≥1 still birth	26 (0.9)	275 (0.9)	0.92 (0.61–1.38)	230 (0.9)	2397 (1.0)	0.94 (0.83–1.09)

Bold font signifies a statistically significant result with regard to the 95% confidence interval (CI).
PL: Pregnancy loss (miscarriage or still birth) RPL: recurrent PL (3 consecutive losses not preceded by a live birth [primary] or preceded by a live birth [secondary]) OR^{adj}: Odds Ratio, adjusted for age and attainment of bachelor's degree. Breast cancer additionally adjusted for parity, age at first live birth, and hormonal contraception ever/never use. Ovarian cancer additionally adjusted for parity and hormonal contraception ever/never use. Endometrial cancer adjusted for parity, hormonal contraception ever/never use, and diabetes.
<5: Data not available for presentation due to less than five observations, estimate therefore not available (n/a).
[a] All invasive cancers, except non-melanoma skin cancer.
[b] Preterm birth, intrauterine growth restriction, preeclampsia or placental abruption.

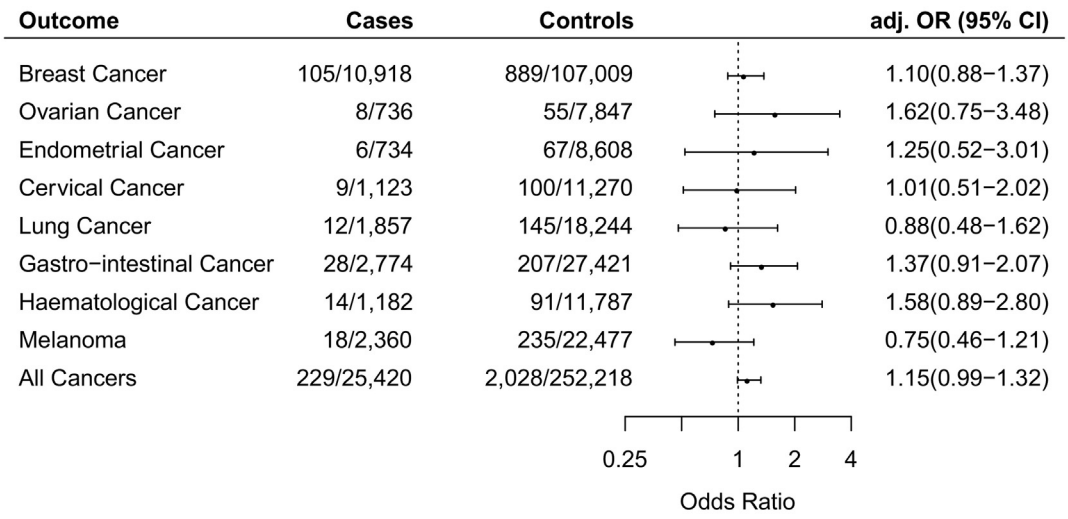

Fig. 2. Odds ratios of different cancers after recurrent pregnancy loss.
Recurrent pregnancy loss defined as three or more consecutive pregnancy losses. The odds ratios were adjusted for age, calendar year, and attainment of a bachelor's degree. Breast cancer additionally adjusted for parity, age at first live birth, and ever/never use of hormonal contraception. Ovarian cancer additionally adjusted for parity and ever/never use of hormonal contraception. Endometrial cancer adjusted for parity, ever/never use of hormonal contraception and diabetes. The scale of the x-axis is logarithmic, and the dashed line signifies an Odds Ratio of 1 (no association). CI: Confidence Interval. Adj. OR: Adjusted Odds Ratio.

voluntary and the involuntarily childless. The latter is likely to include chronically ill and/or infertile women. We found a positive association between the group *never-pregnant* and later ovarian cancer and endometrial cancer, which is in accordance with previous findings [31]. The inverse association between the *never-pregnant* group and breast cancer was, although weak, surprising, as previous studies have demonstrated nulliparity to increase the risk. However, as our study population was relatively young with a mean age of 48.6 years (standard deviation 5.0) the marginally decreased risk of breast cancer among *never-pregnant* group, could be an indicator of the increased risk of breast cancer up to 20 years following a child birth [32]. Contrary to previous studies, our investigation showed women *never-pregnant* to be slightly protected against melanoma [33].

4.4. Strengths and Limitations

The main strength of this study was the population size, including over 28,000 incident cancer events with a full registry-based reproductive history. As our study was nationwide and registry-based, our study was unaffected by recall-bias. Furthermore, the national Danish registries have previously been shown to have a high degree of validity, both for disease and pregnancy. The diagnosis codes for miscarriage, have been validated to have a positive predictive value of 97.4% [34].

Limitations include the underreporting of pregnancy losses, as some women do not seek hospital aid when experiencing early pregnancy loss. However, the underreporting is expected to be equal among cases and controls. Variables of potential interest such as smoking and body mass index were incomplete. To account for this limitation, we provided a sensitivity analysis for lung cancer outcome, restricted to those with smoking data and adjusted for this possible confounder (Supplementary Table S3). Likewise, the outcome of gastro-intestinal cancer was adjusted for body mass index >30 (Supplementary Table S6). Although our study was large, some exposures and outcomes were rare, and the odds ratios consequently with wide confidence limits. We chose to focus our analyses on cancers after the age of 40 to ensure a near complete pregnancy history before a possible outcome of interest occurred, however this choice could limit the finding of a possible association between pregnancy loss and specific cancers at younger age.

In conclusion, our findings did not indicate an association between pregnancy loss and later cancer. For women already suffering from the burden of experiencing multiple pregnancy losses, our findings based on a large and unselected data material is important. Future research may focus on other long-term health risks for women experiencing recurrent pregnancy loss.

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Author Contributions

APM contributed literature search, figures, statistical analyses and wrote the first draft. ØL, HSN and APM conceptualized the study. APM and PE performed data management. All authors made contributions to study design, data interpretation, and revised the manuscript.

Declaration of Competing Interests

Dr. Mikkelsen reports grants from Ole Kirk's Foundation, grants from Copenhagen University Hospital Rigshospitalet's Research Grant, during the conduct of the study. Dr. Egerup has nothing to disclose. Dr. Fynboe Manniche Ebert has nothing to disclose. Dr. Kolte has nothing to disclose. Dr. Nielsen has nothing to disclose. Dr. Lidegaard has nothing to disclose.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.08.017.

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