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Investigating the Mechanisms of Endometrial Cancer Risk in Polycystic Ovary Syndrome: Can UK Biobank Help?

Abstract

Background: UK biobank was set up to investigate the respective contributions of genetic predisposition and environmental exposure to the development of disease and recruited participants between 2006 and 2010. Our aim was to investigate the feasibility of using UK biobank for exploring the association between polycystic ovarian syndrome (PCOS) and endometrial cancer, including the role played by serum IGF-1 levels.

Methods: Publicly accessible and freely available online data in the resource section of the UK biobank website were used to determine the prevalence of self-reported PCOS and for assessing the quality of data on ovarian imaging and serum biomarkers. A literature review was conducted to compare rates of PCOS in UK Biobank with other populations.

Results: UK biobank contains 273,469 women (age range 37-73 years) of whom 643 (0.23%) self-reported PCOS. This was compared with values ranging from 3.1 % to 19.9% obtained from 16 studies picked up by our systematic literature search.

Conclusion: It is feasible to use UK biobank to conduct research into the role of IGF-1 in explaining the association between PCOS and endometrial cancer. More detailed phenotyping of women recruited into the diagnostic group of PCOS is, however, vital to underpin this research. The resulting resource would be excellent for researchers interested in exploring the long-term health risks associated with PCOS.

Keywords: Polycystic; Ovary; Syndrome; UK; Biobank; Endometrial; Cancer; IGF-1

Research Article

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Introduction

Endometrial cancer (EC) is the commonest gynaecological cancer affecting women in the United Kingdom accounting for 43% of all gynaecological cancers. The incidence has increased by over to 60% since the late 1970s. There is an urgent need for research studies looking to improve the diagnosis of EC. The commonest form of EC is type I (well differentiated) and the most frequently altered mutation in type I EC, is the P1K3CA pathway. Elevated IGF-1 and insulin levels have been shown to directly stimulate cell proliferation through activation of the PIK3CA pathway. However, the precise role of elevated IGF-1 levels in the pathogenesis of women with EC is still uncertain. PCOS is the commonest female endocrinopathy and women with PCOS have a 3 to 4 fold increased risk of EC. Pilot data from Nottingham suggests that this is possibly through elevated IGF1 levels [1]. However, the role of IGF1 in increasing EC risk in PCOS is yet to be firmly established as the competing roles of IGF-1 and PCOS on the risk of EC are unclear. We do not know whether their effects are likely to act independently or whether IGF-1 is only a risk factor for EC in women with PCOS.

Fortunately, follow up data from the UK biobank (http://www.ukbiobank.ac.uk/) should now allow a large enough cohort of women who have developed EC from link of UK bio bank with UK cancer registry data. The UK biobank cost £62 million to the UK taxpayer [2] to set up. It is a large long-term study, which is investigating the respective contributions of genetic predisposition and environmental exposure to the development of disease, which recruited participants between 2006 and 2010 [3]. Of the 500,000 participants recruited 273,469 were women. The assessment visit comprised several components. Follow-up is conducted chiefly through linkages to routinely available national datasets.

The UK biobank holds significant potential to facilitate future research into the long-term health risks of women with PCOS including EC. The sample size and wealth of data, including genetic data provides an excellent opportunity for well powered studies to investigate the impact of other potential factors on the pathway between PCOS and EC e.g. oestrogen levels as well as other gynaecological conditions. All of this has the potential to facilitate future therapeutic studies with the aim of reducing the disease burden of EC and other female specific cancers.

It is however important that scientists investigating the long term health risks of EC in PCOS are reassured that results from studies based on UK biobank data are accurate and reliable. This is particularly important with regards to concerns raised about estimating the comorbidity of diseases from the UK biobank, given the low response rate (5.5%) to the questionnaire and selection bias of participants recruited into UK biobank [4].

A literature review of the published papers on the UK biobank website [5] could not identify any previously published studies establishing the feasibility and reliability of using data from UK biobank for research into the long term risks of PCOS or other gynaecological conditions. The aim of this study was to investigate the feasibility and reliability of using UK biobank data for investigating the association between PCOS and EC and in future the role played by serum IGF-1 levels in this association. Our objectives were to critically evaluate the criteria used to establish the diagnosis and prevalence of PCOS and EC and to compare these with the prevalence quoted in the published literature and other large UK based epidemiological studies.

Methods

UK biobank

The study design and methods used by the UK biobank have been previously published [6]. The 502,648 (273,469 women) participants in the UK biobank were assessed between 2006 and 2010 in 22 assessment centres throughout the UK, covering a variety of different settings to provide socioeconomic and ethnic heterogeneity and an urban–rural mix [7]. The assessment visit comprised electronic signed consent; a self-completed touch-screen questionnaire; brief computer-assisted interview; physical and functional measures; and collection of blood, urine, and saliva. Aliquots of different sample fractions are stored in UK biobank's automated laboratory, allowing for a wide range of future assays [8]. We used the freely accessible online data in the resource section of the UK biobank website [9] for this study. Data with the results of responses to a touchscreen questionnaire [10] completed at the assessment centres and questions asked on medical conditions at the verbal interview [11] was downloaded from the UK biobank website onto a Microsoft excel spread sheet. Data on the number of prevalent and incident cases of EC, available ovarian imaging, serum biomarkers and genetic data were also noted.

For responses to the touch screen questionnaire, we focused on the category (Data category 100069), which contained data on female reproductive factors such as age at menarche/menopause. For responses to the verbal interview, we focused on the category (Data category 100074 and field ID descriptions 20001 and 20002) which contained data obtained through a verbal interview by a trained nurse on past and current medical conditions, including type of cancer and other gynaecological illnesses. This data included the number of women reporting ovarian, uterine and cervical pathology.

Exact phrasing of each question is detailed in the resource section and research protocol in the biobank. With the verbal interviews, if participants were uncertain of name of illness, it was described to a trained nurse who placed it in the coding tree. If it could not be placed, a free text description was used instead. These free text entries were examined by a doctor and entered into coding tree if possible. If not, they were marked as "unclassified".

Prevalence of PCOS in other studies and in the literature.

In February 2017, a search on publicly available data was conducted on ongoing longitudinal cohort studies in the UK for data on the prevalence of PCOS in the general population to determine what the prevalence rate was. This could then be compared with the prevalence of PCOS in UK biobank data. These longitudinal cohort studies included the National Survey of Health & Development (NSHD), established in 1946 (http://www.nshd.mrc.ac.uk/), National Child Development Study (NCDS), established in 1958 (http://www.cls.ioe.ac.uk/default.aspx), the 1970 British Cohort Study (BCS70) (http://www.cls.ioe.ac.uk/default.aspx), and the Millennium Cohort Study (MCS), established in 2000 (http://www.cls.ioe.ac.uk/default.aspx). We also searched for publicly available data on the prevalence of PCOS on the websites of the Avon Longitudinal Study of Parents and Children (http://www.bristol.ac.uk/alspac/) and the Born in Bradford Birth Cohort study (http://www.borninbradford.nhs.uk/).

A review of the PubMed website using the key words "polycystic" "ovary" "syndrome" "population" "prevalence" limited to publications over the last 10 years consistent with UK biobank recruitment dates, on 20/2/16 identified 387 "hits". The titles and abstracts of these publications were reviewed and publications where the prevalence of PCOS in general population were investigated using one of the three gold standard criteria (National Institutes of Health diagnostic criteria of PCOS (NIH-1990), Revised Rotterdam 2003 criteria or Androgen Excess Society (AES-2006)) were noted.

We compared the prevalence of PCOS on the UK biobank with the prevalence of PCOS obtained from the published literature and freely accessible data on the website of other ongoing UK cohort studies.

Statistics

Categorical data were summarised as proportions, continuous data were summarised as means and standard deviations. The mean of the prevalence of PCOS derived from the comparative sources (the published literature and freely accessible data on the website of other ongoing UK cohort studies) was used to calculate the expected prevalence of PCOS and this was compared to prevalence in UK biobank. A chi-squared test was used to test whether the differences were present. A p value of less than 0.05 was considered statistically significant.

Results

Table 1, illustrates the demographic characteristics of women recruited into UK biobank. A total of 273,469 women ranging in age from 37 to 73 years were recruited. The mean year of birth was 1951 and the mean age at recruitment 56.5 years. A total of 175864 (64%) of women responded yes to the touch screen question "Have you had your menopause (periods stopped)?"

Table 1: General and female specific demographic characteristics of participants in UK biobank.

Parameter	Number	Percentage
Total number of Participants in UK Biobank	502648	
Age range (years)	37 to 73	
Mean (±SD) year of Birth of all UK Biobank Participants	1951 (±8)	
Ethnicity		
White	497762	99%
Mixed	3063	0.61%
Asian or Asian British	10079	2.01%
Black or Black British	8196	1.63%
Chinese	1634	0.33%
Other Ethnic Group	4667	0.93%
Number of Women	273469	54.41%
Mean age in years (±SD) at Recruitment of all UK Biobank Participants	56.5 (±8)	
Mean age in years (±SD) when Menstrual periods started (menarche)	12.9 (±1.6)	
Number of Women who responded yes to the touchscreen question "Have you had your menopause (periods stopped)?"	175864	64.3% of Women
Mean age in years (±SD) at Menopause (last menstrual period)	49.6 (±5)	
Mean (±SD) Length of Menstrual cycle in days	26.7 (±7)	
Mean (±SD) number of Live Births	1.8 (±1.2)	
Number of Women who had undergone a Hysterectomy	21093	7.7% of Women
Mean (±SD) age at Hysterectomy	43.9 (±8.07)	

Table 2, illustrates the prevalence of gynaecology and early pregnancy problems reported by women recruited into UK biobank (self-reported diagnosis). A total of 643 (0.23%) women reported having polycystic ovaries/ PCOS. Uterine fibroids, ovarian cysts and endometriosis were the three most commonly reported gynaecological conditions with 8470, 4346 and 4252 women respectively reporting these conditions. The UK biobank classification for a self-reported diagnosis of ovarian cysts however also included hydatidiform mole. The most commonly reported female genital tract cancer (Table 3) was cervical (3941 women) followed by uterine /endometrial (1296 women). The UK biobank website has also identified another 354 women who have subsequently developed EC, following initial recruitment, from the linkage of UK biobank data with the cancer registry.

A search of the websites for ongoing longitudinal cohort studies in the UK with data on the prevalence of PCOS in the general population did not identify any publicly available data on the prevalence of PCOS with which to compare UK biobank PCOS prevalence with. Sixteen publications met the criteria used in our literature search (Table 4). The prevalence of PCOS in these studies ranged from 3.1% to 19.9% with a mean prevalence of 10.1%.

The number (643) of women recruited into UK biobank with reported polycystic ovaries/ PCOS was significantly lower than the expected number of women who should have reported this diagnosis (27620) based on the 10.1% mean prevalence of PCOS in the general population in the published literature reviewed ($p < 0.001$). A search of the UK biobank website also revealed that the following biomarkers relevant to our proposed study investigating the links between PCOS and endometrial cancer had been measured. UK biobank has also released imaging data on 5,000 scanned participants. These data include 3T MR images of the brain, 1.5T MR images of the heart and body, DXA images of bone and joint, and carotid ultrasound images. However, ovarian images have not been classified into having polycystic ovaries or not (personal communication).

Table 2: Prevalence of gynaecology and early pregnancy problems reported by women recruited into UK biobank (self-reported).

Parameter	Numbers	Percentage of Women
Number of women Recruited into UK biobank	273469	
Reported cases of Gynaecological Conditions	33885	12.39%
Ovarian Pathology Reported Cases	**5081**	**1.86%**
Unclassified Ovarian Problem (not cyst, mole or PCOS)	93	0.03%
Ovarian Cyst/ Cyst (including Hydatidiform mole)	4346	1.59%
Hydatidiform mole	82	0.03%
Polycystic Ovaries/ Polycystic Ovarian Syndrome	642	0.23%
Uterine Pathology Reported Cases	**17272**	**6.32%**
Unclassified Uterine Pathology (NOT fibroids, polyps, vaginal prolapse or endometriosis)	83	0.03%
Fibroids	8470	3.10%
Polyps	1561	0.57%
Vaginal Prolapse/ Uterine Prolapse	2906	1.06%
Endometriosis	4252	1.55%
Cervical Problems	**1507**	**0.55%**
Unclassified Cervical Pathology (NOT CIN, Cervical polyps and Cervical erosion)	47	0.02%
Cervical Intraepithelial Neoplasia (CIN)/ Precancerous cells cervix	1140	0.42%
Cervical Polyps	207	0.08%
Cervical Erosion	113	0.04%
Other Gynaecological Conditions		
Menorrhagia	1542	0.56%
Pelvic inflammatory Disease	79	0.03%
Dysmenorrhoea	362	0.13%
Menopausal symptoms/ Menopause	480	0.18%
Obstetric Pathology	1784	0.65%
Ectopic Pregnancy	465	0.17%
Miscarriage	1319	0.48%

Table 3: Prevalence of a self-reported diagnosis of female genital tract cancers amongst women recruited into the UK biobank.

Type of the Cancer	Number	Prevalence in UK Biobank	Prevalence in Cancer Registry
Recorded cases of Female Genital tract Cancers	6305	2.31%	
Ovarian Cancer	889	0.33%	1.9%
Uterine / Endometrial Cancer	1296	0.47%	2.43%
Cervical Cancer	3941	1.44%	0.74%
Vaginal Cancer	38	0.01%	0.078%
Vulval Cancer	92	0.03%	0.36%
Fallopian tube cancer	6	0.00%	

Table 4: Studies reporting the prevalence of PCOS in the general population from 2006 to 2016.

Author	Sample Size	Prevalence (%)	Diagnostic Criteria	Country
Balaji S et al. [12]	126	18	Revised Rotterdam 2003 criteria	India
Jiao J et al. [13]	1600	8.25	Revised Rotterdam 2003 criteria	China
Zhuang J et al. [14]	1645	7.1	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	China
Zhuang J et al. [14]	1645	11.2	Revised Rotterdam 2003 criteria.	China
Zhuang J et al. [14]	1645	7.4	Androgen Excess Society (AES-2006).	China
Lauritsen MP et al. [15]	863	16.6	Revised Rotterdam 2003 criteria	Denmark
Rashidi H et al. [16]	646	14.1	Revised Rotterdam 2003 criteria	Iran
Rashidi H et al. [16]	646	12	Androgen Excess Society (AES-2006)	Iran
Rashidi H et al. [16]	646	4.8	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Iran
Li R et al. [17]	16886	5.4	Revised Rotterdam 2003 criteria	China
Gambineri A et al. [18]	519	5.4	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Italy
Gabrielli L et al. [19]	859	8.5	Revised Rotterdam 2003 criteria	Brazil
Yildiz BO et al. [19]	392	6.1	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Turkey
Yildiz BO et al. [20]	392	19.9	Revised Rotterdam 2003 criteria	Turkey
Yildiz BO et al. [20]	392	15.3	Androgen Excess Society (AES-2006)	Turkey
Boyle JA et al. [20]	248	15.3	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Australia
Tehrani FR et al. [22]	1002	8.5	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Iran
Hickey M et al. [23]	244	18.5	Revised Rotterdam 2003 criteria	Australia
Hickey M et al. [23]	244	5	Androgen Excess Society (AES-2006)	Australia
Hickey M et al. [23]	244	3.1	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Australia
Tehrani FR et al. [24]	1126	7.1	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Iran
Tehrani FR et al. [24]	1126	11.7	Androgen Excess Society (AES-2006)	Iran
Tehrani FR et al. [24]	1126	14.6	Revised Rotterdam 2003 criteria	Iran
Ma YM et al. [25]	2111	6.1	Revised Rotterdam 2003 criteria	China
Moran C et al. [26]	150	6.1	National Institutes of Health diagnostic criteria of PCOS (NIH-1990)	Mexico
Moran C et al. [26]	150	6.6	Revised Rotterdam 2003 criteria	Mexico

Discussion

This study found that the 0.23% prevalence of self-reported diagnosis of polycystic ovaries/ PCOS in women recruited into UK biobank was significantly lower than the 10.1% prevalence reported in the general population in the published literature reviewed. Hence, although it should be possible to undertake a study investigating the role played by IGF-1 and other hormones in the association between PCOS and EC using UK biobank data, further work would be required to properly phenotype women

into a diagnosis of PCOS or not, as more women than the 643 with a self-reported diagnosis of PCOS should have the diagnosis. Other studies analyzing the biobank data have demonstrated that self reporting of conditions may not be accurate and may require additional confirmation [13].

Phenotyping women recruited into UK biobank, into a diagnosis of PCOS or not, should be possible given the availability of data on menstrual history, testosterone and SHBG levels in UK biobank. With linkage to GP records, it should be possible to exclude the other causes of hyperandrogenism or oligo / anovulation as required by gold standard diagnostic criteria. The diagnosis would however have to rely on the Androgen Excess Society (AES-2006) criteria given that ovarian images (required for the Rotterdam criteria), have not been classified into having polycystic ovaries or not and the fact that only 5000 (1%) of all the participants in UK biobank have had MRI scans.

The fact that a large number of women recruited in UK biobank were menopausal however poses challenges. The average age of women recruited into UK biobank was 56 years. Although raised androgens in women with PCOS has been shown to persist into the menopause, their menstrual histories may not have been entirely reliable with respect to the diagnosis of the oligomenorhoea or amenorrhoea required for all 3 gold standard criteria (NIH, Androgen Excess and Rotterdam) as many recruited into UK biobank were peri-menopausal. However a large number of women were also premenopausal. If the number of menopausal women is subtracted from the total number of women (273469) recruited into the UK biobank, this still leaves over 97,000 premenopausal women. With a 10.1% prevalence of PCOS, we should have at least 9700 premenopausal women with an objective diagnosis of PCOS.

It is not clear why the prevalence of PCOS was so low in UK biobank. Some possible explanations include issues with the classification into PCOS. From the verbal interviews, women with PCOS may have been inaccurately coded as having ovarian cysts. The validity of a self-reported diagnosis of other medical conditions in UK biobank could however also be called into question considering the difference in prevalence established by self reporting and that according to the cancer registry. Cervical cancer was the most commonly reported female genital tract cancer in UK biobank in contrast to endometrial cancer, which was the highest in the cancer registry. However, taking into account the mean age of women recruited into UK biobank, this might not be unexpected as endometrial cancers are more common in the later stages of life. To substantiate this, a further 354 women have found to have developed endometrial cancer after initial recruitment into the biobank. Many women also self-reported being menopausal (64.3%) when the reproductive symptoms of PCOS may not have been of primary concern. Uterine fibroids, ovarian cysts and endometriosis were the three commonest gynaecological problems reported by women recruited into UK biobank. All this information provides an excellent opportunity for research into the broader health implications of the common gynaecological conditions.

Conclusion

In conclusion, this study suggests that it should be feasible to use UK biobank resource to conduct research into the role of IGF-1 in the association between PCOS and EC, however more detailed phenotyping of the women recruited is vital to underpin this research. If successfully conducted, it would provide an excellent resource for researchers worldwide interested in investigating the long-term health risks and associated biochemical and environmental mechanisms orchestrating these risks in women with PCOS.

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