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ORIGINAL RESEARCH ARTICLE

Previous cancers in women diagnosed with premature ovarian insufficiency: A nationwide population-based case–control study

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Abstract

Introduction: To investigate the occurrence of previous cancer diagnoses in women suffering from premature ovarian insufficiency (POI) and compare it with the general population, shedding light on the association between cancer, cancer treatments, and POI.

Material and methods: We conducted a nationwide case–control study based on registry data from various sources, including the Social Insurance Institution, Finnish Population Information System, and Finnish Cancer Registry spanning from 1953 to 2018. Our subjects comprised all women in Finland who, between 1988 and 2017, received hormone replacement therapy reimbursement for ovarian insufficiency before the age of 40 years ($n = 5221$). Controls, matched in terms of age and municipality of residence, were selected from the Finnish Population Information System ($n = 20\,822$). Our main exposure variable was a history of cancer diagnosis preceding the diagnosis of POI. We analyzed odds ratios (OR) to compare the prevalence of previous cancers in women with POI with that in controls, stratifying results based on cancer type, age

Abbreviations: CI, confidence interval; FCR, Finnish Cancer Registry; HRT, hormone replacement therapy; ICD-O-3, International Classification of Diseases for Oncology, third edition; OR, odds ratio; POI, premature ovarian insufficiency.

at cancer diagnosis, and the time interval between cancer diagnosis and POI. We also assessed changes in OR for previous cancer diagnoses over the follow-up period.

Results: Out of the women diagnosed with POI, 21.9% had previously been diagnosed with cancer, resulting in an elevated OR of 36.5 (95% confidence interval [CI] 30.9 to 43.3) compared with 0.8% of the controls. The risk of developing POI was most pronounced during the first 2 years following a cancer diagnosis, with an OR of 103 (95% CI 74.1 to 144). Importantly, this risk remained elevated even when the time interval between cancer and POI exceeded 10 years, with an OR of 5.40 (95% CI 3.54 to 8.23).

Conclusions: This study reveals that 21.9% of women with POI have a history of cancer, making the prevalence of cancer among these women 27.5 times higher than age-matched controls in the Finnish population. The risk of developing POI is most substantial in the first 2 years following a cancer diagnosis. These findings underscore the role of cancer treatments as an etiological factor for POI and emphasize the importance of recognizing the risk of POI in cancer survivors for early diagnosis and intervention.

KEYWORDS
cancer, cancer survivor, early menopause, premature ovarian insufficiency, young adult cancer

1 | INTRODUCTION

Premature ovarian insufficiency (POI) is defined as amenorrhea for at least 4 months and high follicle-stimulating hormone levels in two separate samples from a woman younger than 40 years.[1] The prevalence of POI is reported to be 1%–3%, and in a recent study, we reported a cumulative incidence of approximately 0.5%.[2,3] The impact of POI on women's health is far-reaching, causing fertility impairment and long-term bone, cardiovascular, and cognitive health deterioration.[4,5]

Genetic, iatrogenic, or autoimmune causes can lead to POI. However, the etiology remains unknown in most patients, even after extensive screening.[6] A genetic etiological factor is found in 7%–30% of patients, and autoimmune diseases have been linked to 4%–30% of POI cases.[4,7,8] In a recent register-based study, we found that 15.9% of POI patients had a genetic disorder or congenital malformation. The overall prevalence of Turner syndrome in our study was 5.13%.[9] Among lifestyle-based risk factors of POI, cigarette smoking has been confirmed to be an independent risk factor for POI in multiple studies.[10–12] Although evidence suggests that low socioeconomic status may influence women's reproductive health, the association between low socioeconomic status and POI is unclear.[13,14]

In many cases of POI, there are no clear warning signs before the loss of ovarian function.[3] However, the adverse effects of cancer treatment options on ovarian reserve have been well-studied.[15,16] The incidence rate of cancers in young women has almost doubled in Finland since 1960 (in 35- to 39-year-olds, from 72.2/100 000 in 1960 to 130.9/100 000 in 2020).[17] Patients receiving cancer treatments can develop POI years after the initial therapies.[18] Chemaitilly et al. reported that that 10.9% of female childhood cancer 10-year survivors had POI by the end of their follow-up up to maximum age of 40 years, and the proportion will be higher when all study participants reach the age of 40.[19] Other studies with very heterogeneous study protocols have reported a wide range of POI prevalence among childhood and adolescent cancer survivors (2.1%–82.8%) after variable intervals between cancer and POI diagnoses.[20,21] Specific cancer treatments, such as radiotherapy of the ovaries, high-dose alkylating agents, or hematopoietic stem cell transplantation, have been associated with a high risk of POI.[19,22,23] Experiments have been conducted to develop tools for assessing the risk of POI in post-pubertal women after chemotherapy, but these tools are not widely used.[24]

Key message

One in five women with premature ovarian insufficiency (POI) had a history of cancer. The prevalence of cancer among women with POI was more than 27 times higher than among controls in the Finnish population. The risk of POI among cancer patients was highest within 2 years of cancer diagnosis.

Although several studies have assessed the risk of childhood cancer survivors developing POI, our knowledge of the prevalence of cancer before POI is limited. Therefore, we aimed to conduct a population-based nationwide study to explore the odds ratio (OR) of previous cancer in women with POI compared with age-matched controls stratified by age at cancer diagnosis and the interval between cancer and POI. Second, we aimed to assess the time window when a patient was most likely to receive a POI diagnosis after developing cancer. Third, we aimed to explore whether the OR for previous cancer varied depending on the calendar period of the POI diagnosis.

2 | MATERIAL AND METHODS

2.1 | Study population

To identify Finnish women with POI, we used reimbursement data for hormone replacement therapy (HRT) from the Social Insurance Institution of Finland. Receiving reimbursement is a two-step process involving two independent physicians. Women with POI in Finland receive 100% reimbursement for HRT medications until the age of 50 years. The reimbursement is applied by the treating physician at the time of POI diagnosis, regardless of whether the patient initiates HRT treatment at that time or not. The reimbursement criteria and their changes over time have been described in detail in a previous article.[2] These requirements have always been aligned with international diagnostic criteria.

We identified 5221 women who were granted the right to POI medication reimbursement between 1988 and 2017 at ages less than 40 years. We excluded from both cases and controls women with a history of bilateral oophorectomy for benign reasons but included women with bilateral oophorectomy performed for cancer treatment. We also excluded transgender patients, who in Finland have the same code for reimbursement for HRT. Four population controls for each POI case were selected from the Finnish Population Information System of the Digital and Population Data Services Agency, matched for month and year of birth and municipality of residence. The controls also had to be alive and living in Finland when reimbursement was granted to the respective case (index date). We excluded also controls who had a history of bilateral oophorectomy ($n=49$). The total number of controls was 20 822. We combined information from different registries using unique personal identity codes available to all Finnish citizens and permanent residents.

2.2 | Finnish Cancer Registry

We used data from the Finnish Cancer Registry (FCR) to determine the diagnoses of all cancers in cases and controls from 1953 to 2018. The FCR collects information from clinical and laboratory sources, including diagnosis dates and characteristics. If cancer is mentioned in a death certificate sent to Statistics Finland, the information is forwarded to the FCR. In validation studies, the rate of reporting malignancies to the FCR was close to 100%.[25,26]

Our analyses included all cancer diagnoses before the index date, classified using the topography, morphology and, if necessary, behavior codes of the International Classification of Diseases for Oncology, third edition (ICD-O-3). The diagnostic codes for each cancer category included and excluded in this study are listed in Table S1.

2.3 | Statistical analyses

We calculated OR and 95% confidence intervals (CI) for the cancer groups of main interest using binary logistic regression analysis. Groups of primary interest included cancers that commonly require treatments with a risk for POI. We did not calculate OR for smaller groups if there were not enough cancers in the control group, or if clinicians would not see it as relevant to apply for HRT reimbursement. This is true for estrogen-dependent cancers or cancers with minimal life expectancy. This bias would lead to too low OR estimates. However, these cancer diagnoses were included in the statistical analyses for overall OR (Tables 3 and 4). Due to the Finnish data protection policy, we cannot report the exact number of cancers if there were one to four cases or controls in a specific subgroup. The list of cancer categories that were studied but not reported in this paper because there were no cases among our study participants can be found in Table S1.

We calculated OR for childhood and adulthood cancers using the World Health Organization's definition of childhood cancer (cancer diagnosed at the age of 0–17 years) but also estimated separately the frequencies of cancers diagnosed in prepubertal children (0–9 years old) and older children (10–18 years old).

Furthermore, we calculated OR for previous cancer in patients with POI stratified by the time interval between cancer diagnosis and the index date (<2, 2–4, 5–9, and ≥10 years). In this analysis, we excluded POI cases and their matched controls with age below 17 years on the index date because in such young individuals late-onset menarche may have caused a delay in recognizing POI and granting reimbursement for its treatment. In Finland, examinations for primary amenorrhea are initiated in the public healthcare system at the age of 16 years. We calculated OR by time interval for all cancers and separately for hematologic malignancies and lymphomas because they were the largest subgroup in our analysis.

To determine whether the prevalence of preceding cancer diagnoses among the POI patients varied over time, we calculated the prevalence stratified into 5-year calendar periods from 1988–1993 to 2013–2017. To adjust for changes in age distribution at POI diagnosis, we standardized the period-specific rates to the distribution of age at POI diagnosis of cases in 2013–2017. We also calculated the OR for previous cancers by 5-year calendar periods of the index date using binary logistic regression.

The data were processed using RStudio (Rstudio Inc.) and SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary NC, USA), and the statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at p values less than 0.05. The data were analyzed and reported in accordance with the STROBE statement.

3 | RESULTS

Of the 5221 patients with POI, 1146 (21.9%) had a cancer diagnosis before the index date (reimbursement for POI), whereas this proportion among controls was 0.8% ($n=159$). Of the POI patients with previous cancer diagnoses, 5.0% ($n=57$) had two or more cancer diagnoses compared with 1.3% ($n=2$) of the controls. The proportions of childhood cancers to all cancers in the cases and controls were virtually

TABLE 1 Frequencies and percentages of cancers diagnosed before the index date (receiving reimbursement for premature ovarian insufficiency [POI]) among women with POI (cases) and their matched controls and odds ratios (OR) with 95% confidence intervals (CI) for having had a cancer diagnosis before POI by cancer type.

	Cases			Controls		
Cancer type	*n* (%)	Age at cancer diagnosis: median (range)	Years from cancer to index date, median (range)	*n* (%)	Age at cancer diagnosis: median (range)	OR (95% CI)
Hematological malignancy or lymphoma	310 (5.9)	26.1 (1.0–39.4)	1.6 (0.01–31.7)	18 (0.1)	19.0 (8.3–36.9)	73.0 (45.3–117)
Myeloid leukemia	127 (2.4)	25.8 (1.0–39.0)	0.98 (0–32)	1–4 (<0.02)	N/A[a]	260 (64.2–1049)
Acute lymphoblastic leukemia and non-Hodgkin lymphoma	132 (2.5)	27.9 (1–39.0)	1.65 (0.1–19)	9 (0.04)	20.9 (8.3–36.3)	60.0 (30.3–117)
Hodgkin lymphoma	50 (1.0)	25.5 (12.0–39)	4.7 (0.4–20.2)	5 (0.02)	16.4 (14.7–31.2)	40.3 (16.0–101)
Cervical cancer	206 (3.9)	35.1 (21.6–39.8)	0.28 (0.03–10.6)	1–4 (<0.02)	N/A	213 (79–575)
Invasive ovarian cancer	259 (5.0)	33.3 (9.1–39.9)	0.39 (0.05–18.6)	1–4 (<0.02)	N/A	271 (101–729)
Borderline ovarian tumor	110 (2.1)	35.3 (17.0–40.0)	0.32 (0–19.0)	1–4 (<0.02)	N/A	112 (41.3–304)
Other gynecological cancers	69 (1.3)	35.6 (1.0–39.3)	0.48 (0.03–30.5)	1–4 (<0.02)	N/A	139 (34.2–569)
Brain and central nervous system tumor or peripheral nervous system cancer	35 (0.7)	15.0 (0.4–8.0)	4.07 (0.64–18.2)	6 (0.03)	30.4 (6.4–37.8)	23.4 (9.8–55.7)
Colorectal cancer	58 (1.1)	34.9 (20.4–39.4)	0.90 (0.1–18.7)	8 (0.04)	32.9 (12–40)	29.2 (13.9–61.2)
Bone, connective tissue, and soft tissue cancer	34 (0.7)	19.7 (0.5–39.0)	2.02 (0.14–14.4)	6 (0.03)	23.4 (0–32.9)	22.7 (9.5–54.2)

[a]Not applicable, data not allowed to be presented.

equal (11.7% vs. 12.6%). Of the POI patients, 1.1% ($n=60$) were diagnosed with cancer before the age of 10 years, and 1.4% ($n=74$) were between 10 and 17 years of age at the time of cancer diagnosis compared with 0.03% ($n=6$) and 0.07% ($n=14$) of the controls. The OR for having a previous cancer diagnosis at any age before the index date was 36.5 (95% CI 30.9 to 43.3). The OR for having had a cancer diagnosis before age of 18 was 27.4 (95% CI 17.1 to 43.9), and for a cancer diagnosis at age 18 or older it was 35.8 (95% CI 29.9 to 42.8).

The numbers and percentages of cancers in the categories of primary interest are reported in Table 1. We also report in Table 1 the OR for previous cancer diagnoses in POI patients compared with controls, the median age for cancer diagnosis and the median for the time interval between cancer and POI. In women with POI, 27.1% of the cancers were hematological malignancies or lymphomas, 18.0% were cervical cancers, 22.6% were ovarian cancers, and 3.1% were brain tumors. For descriptive purposes, Table 2 shows the numbers of cases and controls in those cancer categories and specific subgroups for which OR calculations comparing women with POI with the controls were not performed.

The median intervals from cancer diagnosis to granted POI medication reimbursement were 0.59 years (standard deviation [SD] 2.8; range 0.01–19.5 years) in adults and 4.8 years (SD 5.4; range 0.05–23.0 years) in children. The OR for POI diagnosis was highest in the first 2 years after cancer but was still elevated even after 10 years of cancer diagnosis (Table 3). In this analysis, we calculated the lag from the first cancer diagnosis to the index date. The results were virtually identical when individuals with more than one cancer were excluded.

The prevalence of cancer diagnoses preceding POI increased from 17.9% for POI cases in 1988–1992 to 25.1% in 2013–2017. At the same time, the respective prevalence of cancers among the controls increased from 0.52% in 1988–1992 to 1.07% in 2013–2017. The OR for previous cancer in women with POI has remained high during the whole follow-up period. The OR for a previous cancer occurrence was highest between 2003 and 2007 (OR 45.3, 95% CI 28.9 to 71.1) (Table 4).

4 | DISCUSSION

In this nationwide study population of 5221 women with POI, the prevalence of cancer before POI diagnosis was 21.9%. In age-matched controls, the prevalence of cancer was 0.8%. The prevalence of previous cancer diagnoses increased during the follow-up period in women with POI and controls. The rise in prevalence is in

TABLE 2 Frequencies and percentages of cancer subgroups diagnosed before the index date (reimbursement for premature ovarian insufficiency [POI]) among women with POI (cases) and their matched controls.

	Cases		Controls	
Cancer type	***N***	**%**	***n***	**%**
Cervical cancer				
Squamous cell carcinoma	173	3.3	1–4	<0.02
Adenocarcinoma	11	0.2	1–4	<0.02
Other or unspecified histology	22	0.4	1–4	<0.02
Ovarian cancer				
Epithelial cancer	195	3.7	1–4	<0.02
Germ cell tumor	38	0.7	1–4	<0.02
Granulosa cell tumor	17	0.3	-	-
Other or unknown histology	11	0.2	-	-
Other cancers				
Medulloblastoma	15	0.3	-	-
Low-grade brain tumors	1–4	<0.4	1–4	<0.02
Ear, nose, throat, or eye cancers	11	0.2	1–4	<0.02
Cancers of the upper gastrointestinal tract	12	0.2	5	0.02
Lung cancer	9	0.2	1–4	<0.02
Breast cancer	11	0.2	28	0.1
Urinary tract cancer	10	0.2	8	0.04
Endocrine gland cancer	24	0.5	26	0.1
Skin melanoma	8	0.2	13	0.1
Other malignant skin cancers	18	0.3	24	0.1
Cancer with an unknown location	7	0.1	-	-

Note: The odds ratios (OR) were not calculated for these groups either because there were not enough cancers in the control group or if there was a potential bias that would lead to too low OR estimates (estrogen-dependent cancer or cancers with minimal life expectancy).

TABLE 3 Odds ratios (OR) and 95% confidence intervals (CI) for premature ovarian insufficiency (POI) by the time interval between cancer diagnosis and index date (excluding cases diagnosed with POI at an age under 17 years).

	Any cancer				Hematological malignancy or lymphoma			
Time from cancer to the index date	Cases (*n*)	Controls (*n*)	OR	95% CI	Cases (*n*)	Controls (*n*)	OR	95% CI
<2 years	801	37	103	74.1–144	169	1–4	349	86.5–1408
2–4 years	146	37	16.2	11.3–23.3	58	0	N/A[a]	N/A
5–9 years	86	45	7.74	5.39–11.1	33	7	18.9	8.36–42.8
≥10 years	51	38	5.40	3.54–8.23	23	8	11.5	5.15–25.8
Any	1084	157	35.2	29.6–41.7	283	17	70.4	43.1–115

[a]Not applicable.

TABLE 4 Odds ratios (OR) and confidence intervals (CI) for a cancer diagnosis before the index date among patients with premature ovarian insufficiency by a 5-year period.

Period of POI medicine reimbursement acceptance	Cases (*n*)	Controls (*n*)	OR	95% CI
1988–1992	187	25	35.9	23.5–54.8
1993–1997	210	29	35.4	23.9–52.6
1998–2002	215	31	35.0	23.8–51.4
2003–2007	189	22	45.3	28.9–71.1
2008–2012	181	25	39.9	26.0–61.4
2013–2017	164	27	32.0	21.1–48.7

Abbreviation: POI, premature ovarian insufficiency.

line with the rising rates of cancer diagnoses among young women in the general population over the last few decades.[17] The OR for previous cancer in POI patients remains very high compared with the general population. The risk of POI is highest within 2 years of cancer diagnosis, but it is elevated even when cancer is diagnosed more than 10 years before POI.

The strength of this study is that it provides novel information about the prevalence of cancers before POI diagnosis on a large scale. In our research, we were also able to demonstrate that women with POI exhibit higher odds not only for hematological malignancies and lymphomas, but for various other preceding cancers, such as colorectal cancer and bone and connective tissue cancers, compared with controls. Our study also provides novel information about the prolonged elevated risk for POI. Furthermore, one of the strengths of our study are the highly reliable registry-based POI and cancer diagnoses used. To our knowledge, no previous population-based study has investigated the prevalence of previous cancer in women with POI. However, studies investigating the prevalence of POI in female cancer survivors in specific cancer types exist, and they have reported highly variable figures.[20,21,27,28]

Our study has some limitations. Details on cancer treatments are not available in the registers used. The gonadal effects of cancer treatments are multifactorial, depending on the cancer site, treatment protocol (chemotherapy, radiotherapy, or both), gonadotoxicity, cumulative dose of chemotherapy agents, age at the time of treatment, and individual variability in treatment response. Cancer treatments may damage the ovarian reserve in many ways: they can cause direct damage to the growing follicles or primordial follicles, inflammation, atresia, stromal damage, and damage to the vasculature.[22] The most common cancers before POI in our study were hematological malignancies and lymphomas, ovarian cancers, and cervical cancers. In a recent study of female childhood cancer survivors, patients who needed induced puberty were 5.3%, and 9.3% of the survivors needed estrogen replacement therapy. Patients with hematopoietic stem cell transplantation had an OR of 18.5 (95% CI 10.8 to 31.8) for estrogen replacement therapy.[29] During our follow-up period, there have been no drastic changes in treatment protocols in the most common cancer groups. In hematological malignancies, for example myeloid leukemia, most of the adults and a majority of the childhood cancer patients had received a stem cell transplant during our follow-up period. In acute lymphoblastic leukemia, treatment protocols have changed so that central nervous system radiotherapy has not been part of the treatment protocol since 2008.[30] In gynecological cancer treatments, not much has changed during our follow-up period in terms of ovarian toxicity. In young surgically treated cervical cancer patients, ovaries are spared, but they receive chemotherapy and pelvic radiation, which predispose to POI.[31]

Moreover, the POI diagnoses were based on HRT reimbursement in this study. For some cancer patient groups, clinicians do not consider it relevant to apply for HRT reimbursement. This is especially the case for estrogen-dependent cancers, such as breast cancer. The cumulative risk for a Finnish woman to receive a breast cancer diagnosis until the age of 40 years in 1953–2017 was 0.32%,[17] and our results do not significantly differ from these results at 0.2% of breast cancer cases within POI patients and 0.1% within controls. In a population-based study by Flatt et al., the adjusted relative risk of POI after breast cancer was 4.32 (95% CI 3.84 to 4.86) in adolescent and young adult women when the diagnosis of POI was based on the ICD-9 code for menopause before the age of 40.[27] In ovarian cancer patients, especially in those with high-grade serous epithelial tumors, estrogen is contraindicated in clinical practice. For young women with mucinous tumors or other tumor types than serous epithelial ovarian cancer, HRT initiation has been more liberal (as these cancer types are often not estrogen-dependent and they are more common in younger patients).[31] It is therefore likely that in our study population the mucinous epithelial ovarian cancers

are over-represented compared with the serous epithelial tumors. The potential bias is that we have missed some of these patients, and therefore we might underestimate the difference between POI patients and controls. Moreover, it is often not meaningful to apply for HRT reimbursement for cancer patients with a minimal life expectancy, such as lung cancer patients. This bias may also have decreased the contrast between women with POI and controls. In cervical cancer patients, who develop POI, HRT use is not contraindicated.[31]

Our study is a register-based case–control study with four-fold population controls, adjusted with month of birth and municipality of residence. In our previous study, we determined that the socioeconomic status or level of education did not significantly differ between cases and controls.[2] However, we did not have access to lifestyle-based confounders, such as cigarette smoking. Therefore, caution should be exercised when interpreting the results.

Clinicians should be aware of the high risk of POI in cancer survivors to ensure the early diagnosis and initiation of HRT in patients who develop POI after cancer. They should also discuss the risk of POI with all girls and women diagnosed with cancer and offer them relevant counseling about the symptoms of POI and its impact on fertility and general health. All women diagnosed with cancer should be informed about fertility preservation methods, among which cryopreservation of oocytes or embryos is the most common strategy for young women. It should be noted, however, that cryopreservation of oocytes, embryos, or ovarian tissue does not protect ovarian tissue or reduce the risk of POI. Even for women not interested in fertility preservation, protecting their ovaries during cancer treatment with gonadotropin-releasing hormone agonists whenever possible to minimize the risk of POI is recommended for future health.[32] Therefore, developing cancer treatments with low ovarian toxicity is vital.

5 | CONCLUSION

More than one in five women diagnosed with POI has a history of cancer. Acknowledging the high risk of POI in cancer survivors, even more than a decade after the cancer diagnosis, is of utmost importance for enabling counseling, fertility preservation, and early diagnosis and treatment in these women. With these interventions, healthcare professionals can promote cancer survivors' health and quality of life.

AUTHOR CONTRIBUTIONS

All authors participated in planning the study design. Paula Pesonen and Heidi Silvén performed the data analyses. The article was drafted by Heidi Silvén, Susanna M. Savukoski, Paula Pesonen, Maarit Niinimäki, and Eero Pukkala. All authors commented and discussed the article.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to declare.

ETHICS STATEMENT

This study was approved by the Finnish Institute for Health and Welfare (THL/1973/5.05.00/2019), the Social Insurance Institution (135/522/2018), and the Digital and Population Data Services Agency (VRK 4304-2019-2). Anonymization was performed before the analyses; hence, identifiable personal data could not be accessed. According to the national guidelines, ethics committee approval was not required due to the study's registry-based nature.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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