Environmental Research 240 (2024) 117374

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Risk of breast cancer in daughters of agricultural workers in Denmark

Julie Elbaek Pedersen [*], Johnni Hansen

The Danish Cancer Institute, Danish Cancer Society, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Occupational health
Environment
Farming
Pesticides
Parental exposure
Breast cancer

ABSTRACT

Objectives: Agricultural workers face unique occupational hazards such as pesticide exposure, which has been associated with breast cancer. However, research considering the association between parental agricultural work and breast cancer in female offspring is lacking. Therefore, the aim of the present nested case-control study was to explore this association.

Methods: The Danish Cancer Registry was utilized to identify women diagnosed with primary breast cancer. A total of 5587 cases were included in the study, and for each case, 20 cancer-free female controls were selected, matched on year of birth. It was a requisition that both cases and controls were born in Denmark and that either maternal or paternal employment history was available.

Results: Adverse associations were consistently noted for different time windows of maternal employment in "Horticulture" and breast cancer. Inverse associations were observed for paternal employment in most of the examined agricultural industries, although a small increased risk was indicated for perinatal employment in "Horticulture".

Furthermore, maternal preconceptional employment in "Horticulture" was observed to increase the risk of ER positive tumors (odds ratio [OR] = 1.79, 95% confidence interval [CI]: 1.13–2.85, whereas parental perinatal employment was linked to an elevated risk of ER negative tumors (maternal employment: OR = 2.48, 95% CI: 1.18–5.21; paternal employment: OR = 1.62, 95% CI: 0.70–3.77).

Conclusions: The present study indicates that maternal horticultural employment in different potential susceptible time windows may elevate the risk of breast cancer subtypes in daughters. These findings need to be reproduced in future prospective cohort studies, including information on e.g., pesticide exposure withing agricultural job categories and lifestyle factors.

1. Introduction

Breast cancer poses a significant global health concern by being the most diagnosed cancer in women. Over the last half of the 20th century, there has been a substantial increase in breast incidence rates. In the past few decades, the incidence in most Western countries has either stabilized or declined. However, the occurrence of estrogen receptor-positive tumors continues to show an upward trend (Sung et al., 2021). Established risk factors include age, sex, family history of breast cancer, genetics, radiation, use of oral contraceptives, hormone replacement therapy (HRT), and reproductive factors such as nulliparity, delayed age at first birth, early age at menarche, and late age at menopause. Lifestyle factors like physical inactivity and alcohol consumption are also associated with an elevated risk of breast cancer (Labrèche et al., 2014). However, not all cases of breast cancer can be attributed to these known risk factors (Mesko et al., 1990).

Emerging evidence suggests that environmental exposures, particularly endocrine disrupting compounds (EDCs), may play a significant role in breast cancer development (Gray et al., 2017; Rodgers et al., 2018). EDCs are chemicals that can mimic, disrupt, or interfere with the normal functioning of the endocrine system (Rodgers et al., 2018). Some pesticides, including herbicides, insecticides, and fungicides, possess such properties (Cardona and Rudel, 2021).

Several pesticides with widely varying ADME (Absorption, Distribution, Metabolism, and Excretion) properties have been demonstrated to induce mammary gland tumors or alter development in animals (Rudel et al., 2007; Yang et al., 2020; Cardona and Rudel, 2020). A recent study by Cardona and Rudel provides an updated list of pesticides with breast cancer relevant endocrine activity (Cardona and Rudel, 2020). Some epidemiological studies have also reported associations between organophosphate pesticides (OPs) and breast cancer (Yang et al., 2020). Evidence further suggests that the prenatal period

* Corresponding author.The Danish Cancer Institute, Danish Cancer Society, Strandboulevarden 492100 Copenhagen Ø, Denmark.
E-mail address: juliep@cancer.dk (J. Elbaek Pedersen).

https://doi.org/10.1016/j.envres.2023.117374
Received 22 June 2023; Received in revised form 9 October 2023; Accepted 9 October 2023
Available online 20 October 2023
0013-9351/

represents a critical window of vulnerability to pesticides and other EDCs (Nicolella and de Assis, 2022; Terry et al., 2019). This is supported by epidemiological studies indicating that developmental exposure to dichlorodiphenyltrichloroethane (DDT) increases the risk of breast cancer in adulthood (Cohn et al., 2015, 2019; Chang et al., 2018). Possible biological mechanisms include alterations in maternal hormone levels that regulate normal development of the fetal mammary gland (Terry et al., 2019). Developmental exposure to specific pesticides may also lead to epigenetic modifications of genes associated with breast cancer risk (Wu et al., 2020). It has also been proposed that parental environmental exposure can influence disease risk in children through epigenetic inheritance (Nicolella and de Assis, 2022).

Historically, the United States and Europe were hotspots for environmental discharges of several synthetic organochlorine pesticides, particularly during the 1960s and 1970s (Li et al., 2023). Although many of these pesticides have been banned in Western societies since the late 1970's, some continues to be used in other parts of the world (van den Berg, 2009). Moreover, many of these chemicals exhibit lipophilic properties and persist in the environment as pollutants, circulating through ecosystems (Blair et al., 2015). Several pesticides causing mammary tumors or altering mammary gland development in experimental animal models were only recently banned during the early 2000's in European Union member nations, including Denmark (European Chemicals Agency, 2023), and quite a few are still used in the US (Cardona and Rudel, 2020).

A large body of literature has evaluated the association between agricultural work and breast cancer, however, these have overall yield inconsistent findings (Coogan et al., 1996; Katuwal et al., 2018; Sritharan et al., 2019; Settimi et al., 1999; Khalis et al., 2019; Brophy et al., 2006, 2012; Band et al., 2000; Mills and Yang, 2005; Pedersen and Hansen, 2022). A recent meta-analysis based on the international consortium of agricultural cohort studies (AGRICOH) indicated a deficit for breast cancer (Togawa et al., 2021), which may be attributed to healthier lifestyle habits in this working population (Thelin et al., 2009; Stiernström et al., 2001; Gallagher et al., 1984). To the best of the authors' knowledge, no studies have examined parental agricultural work, potentially entailing a high risk of pesticide exposure, and risk of breast cancer in female offspring. Consequently, there is a notable research gap in agricultural research regarding susceptibility time windows and breast cancer. Addressing this gap could provide valuable new evidence.

Agriculture remains a significant sector in Denmark, spanning over 60 percent of the land (Statistics Denmark, 2023). Moreover, Denmark offers a unique opportunity to access individual-level data from comprehensive registries, enabling large-scale studies on parental employment history and subsequent health outcomes in next generations. Accordingly, the objective of this study was to investigate the risk of breast cancer in daughters of workers employed in various Danish agricultural industries.

2. Methods and material

The present nested case-control study was based on an already established data-set, including information obtained from national Danish registries and databases, i.e., the Danish Cancer Registry (Gjerstorff, 2011), the Danish Breast Cancer Group (DBCG) database (Blichert-Toft et al., 2008), the Danish Civil Registration System (DCRS) (Pedersen, 2011), and the Supplementary Pension Fund Registry (Hansen and Lassen, 2011). Individual-level linkage of information was done by use of the unique 10-digit personal identification number (PIN), which has been assigned to all Danish residents at birth or immigration since 1968 by DCRS, which is considered a complete and updated national register entailing information on all Danish residents (Pedersen, 2011). The establishment of the dataset has previously been described in detail (Pedersen and Hansen, 2023) and is therefore only summarized here.

2.1. Cases and controls

The national Danish Cancer Register, established in 1942, was utilized to identify women diagnosed with breast cancer ≤2016 (Gjerstorff, 2011). Parental information was obtained by record linkage to DCRS (Pedersen, 2011). To be eligible, cases were required to have either maternal or paternal employment information (see next section). However, cases themselves were not required to have registered employment history. As parental employment history was accessible from 1964 onwards, cases had to be born in Denmark in 1965 or later, allowing an assessment of parental employment prior to birth. As a result of this process, the total number of cases was 5587 and they were born between 1965 and 1994. Age at breast cancer diagnosis was thus limited to 51 years or younger, primarily representing cases with premenopausal breast cancer (Gottschalk et al., 2020; Kroke et al., 2001). The clinical Danish Breast Cancer Group (DBCG) (Blichert-Toft et al., 2008) was subsequently used to retrieve information on breast tumors by hormonal subtype, i.e., estrogen receptor (ER) status, during 1978–2015, which was available for 4589 (82%) of cases. Controls, all of whom had either paternal or maternal employment information, were born in Denmark, were breast cancer free and alive at the index date of the corresponding case, were randomly selected from the DCRS by applying the incidence density sampling procedure (1:20) and matched on sex and year of birth.

2.2. Assessment of parental employment

Data on individual-level job records spanning from 1964 to 2014 was collected from the Supplementary Pension Fund for the study population consisting of cases and controls and their identified parents. The Supplementary Pension Fund is a register that holds employment information for all wage earners in Denmark and it was established in 1964. Membership is mandatory for all employees. Each company in Denmark is assigned an industry code (in Danish: Danmarks Statistiks Erhvervsgrupperingskode, DSE), according to an extended version of the International Standard Industrial Classification of all Economic Activities (ISIC) (International standard industrial classification, 1990). As this classification underwent changes during the study period, we utilized converted codes that corresponded to the original five-digit "Erhvervsgrupperingskode 1977" (DSE-77 code) allocated by Statistics Denmark to ensure consistency (Hansen and Lassen, 2011).

In the present study, agricultural industries classified by the DSE coding system and with minimum 5 cases and controls included: "Agriculture, unspecified" (11,101), "Horticulture" (11,102), "Farming, crops" (11,111), "Farming, livestock" (11,112), and "Agricultural machinery stations" (11,201). We also examined all agricultural industries combined ("Overall work in agriculture", 11,101–11,209) and each industry separately (See Supplemental Table 1 for a specification of the agricultural industries 11,101–11,209). We examined different aspects of parental employment in agriculture, including never vs. ever employment. In conducting these analyses, our aim was to capture relevant time periods of employment; employment history for mothers was therefore restricted to ever work until one year after birth, thus capturing periods of preconception, pregnancy and lactation. Employment history for fathers was restricted to ever work until birth and thus captured the period prior to conception, of spermatogenesis and during pregnancy with the potential of para-occupational take-home exposure from agricultural work. Furthermore, we investigated employment that occurred specifically before one year leading up to birth, thus encompassing preconceptional work. We also explored employment during the perinatal period, defined as one year prior to birth until one year after birth for mothers, and one year prior to birth for fathers. Carrying out additional analyses relating to parental agricultural employment post childbirth was unfeasible, given that most parents working in agriculture had been employed during this period.

2.3. Covariates

A directed acyclic graph (DAG) illustrating potential confounders is provided in Supplementary Fig. 1, based on prior knowledge of breast cancer. Information on factors in cases and controls, including geographical residence at birth (urban, small town, rural), birth order (first, second, third or later), parity at the index date (0, 1–2, ≥3 children), and age at first live birth (no children, <25, 25–29, 30–34, ≥35 years), was obtained from DCRS (Pedersen, 2011). Family history of breast cancer in the mother or sister(s) was determined using data from the Danish Cancer Register (Gjerstorff, 2011). We also assessed employment in agriculture among cases and controls with registered employment history (never vs. ever employment).

Regarding parental factors, family socioeconomic status (SES) was assessed by considering the highest SES status of either the mother or the father. Information on the last known job title obtained from DCRS was used to categorize SES into five groups: unskilled workers, skilled workers, shorter education, middle education, and academics, according to the definition provided by the Danish Institute of Social Sciences (E.J. H. et al., 1984). Cases and controls with missing information on parental job title were allocated to a separate category. Additionally, parental age at birth (<25, 25–29, 30–34, ≥35) was included from the registry. To account for potential healthy worker selection effects in parents, we linked employment history records to the NOCCA-DANJEM (Kauppinen et al., 2009) to assess work-related physical activity. This involved categorizing individuals as either never vs. ever having worked in a job with "heavy or rather heavy physical work".

2.4. Statistical analysis

Separate analyses were conducted for maternal and paternal data, and conditional logistic regression was used to calculate odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). The risk of breast cancer and specific hormonal subtypes associated with parental work in agricultural industries was assessed using two sets of models: a minimally adjusted model that included year of birth (matching factor), and a fully adjusted model that incorporated all potential confounders without missing data. Hereafter, we conducted complete case analyses only including women with data on family SES. In additional analyses, the study population of women was constrained to those having both maternal and paternal employment history, which permitted mutual adjustment for paternal and maternal employment in agriculture. Lastly, we investigated interactions between ever paternal and maternal employment in the agricultural industries.

Stata Statistical Software v 16.1 (StataCorp, College Station, TX, USA) was applied to conduct all analyses. No informed consent from the study population was required as the study was purely registry-based.

3. Results

Among the cases, a total of 4569 had employment information on both parents, 520 had information only on paternal employment, and 498 had information only on maternal employment. There were no noticeable differences between cases and controls in terms of most explored characteristics, although parental age at birth of cases tended to be slightly higher compared to controls. Additionally, several well-established risk factors for breast cancer were more prevalent in cases than in controls, including higher age at first live birth and a family history of breast cancer. Higher parity was also observed to be more prevalent in cases, which corresponds to evidence suggesting that higher parity increases the risk of early-onset breast cancer (Anderson et al., 2014a). A significant proportion of cases were born in earlier time periods, were over the age of 40 at the time of diagnosis, and a larger percentage had received a diagnosis of ER positive tumors (Table 1). The proportion of cases and controls who had registered employment in various agricultural industries generally exhibited a resemblance

Table 1
Characteristics of the study population of women, including parental information.

	Women for whom maternal employment history were available		Women for whom paternal employment history were available	
	Cases N = 5067	Controls N = 96,688	Cases N = 5089	Controls N = 100,085
	(%)	(%)	(%)	(%)
Birth order				
First	2291 (45.2)	43,134 (44.6)	2269 (44.5)	44,306 (44.3)
Second	1782 (35.2)	34,211 (35.3)	1795 (35.3)	35,224 (35.2)
Third or later	994 (19.6)	19,343 (20.1)	1025 (20.2)	20,555 (20.5)
Place of birth				
Urban	1845 (36.5)	36,143 (37.3)	1827 (35.9)	36,479 (36.4)
Small town	2007 (39.6)	37,417 (38.8)	2029 (39.9)	39,184 (39.2)
Rural	1215 (23.9)	23,128 (23.9)	1233 (24.2)	24,422 (24.4)
Age at first live birth				
No children	1737 (34.2)	34,292 (35.4)	1762 (34.6)	34,998 (34.9)
<25	947 (18.7)	21,157 (21.8)	951 (18.6)	22,673 (22.7)
25–29	1548 (30.6)	27,939 (28.9)	1552 (30.5)	28,900 (28.9)
30–34	737 (14.6)	11,352 (11.8)	720 (14.2)	11,588 (11.6)
≥35	98 (1.9)	1948 (2.1)	104 (2.1)	1926 (1.9)
Parity				
0	1737 (34.2)	34,292 (35.4)	1576 (34.5)	30,345 (35.6)
1–2	3163 (62.4)	58,326 (60.4)	2844 (62.3)	51,111 (60.1)
≥3	167 (3.4)	4070 (4.2)	149 (3.2)	3577 (4.3)
Family history of breast cancer				
No	4203 (82.9)	87,743 (90.7)	4294 (84.4)	91,876 (91.8)
Yes	864 (17.1)	8945 (9.3)	795 (15.6)	8209 (8.2)
Family socioeconomic status				
Academics	545 (10.7)	10,595 (10.9)	558 |(10.9)	11,124 (11.1)
Middle education	734 (14.5)	14,815 (15.4)	739 (14.5)	15,143 (15.2)
Shorter education	955 (18.9)	17,880 (18.5)	944 (18.6)	18,328 (18.4)
Skilled	1582 (31.3)	30,732 (31.8)	1590 (31.3)	32,005 (31.9)
Unskilled	887 (17.5)	18,398 (19.0)	935 (18.4)	20,058 (20.0)
Missing	364 (7.1)	4268 (4.4)	323 (6.3)	3427 (3.4)
Parental age at birth				
<25	2240 (44.2)	45,108 (46.7)	1283 (25.2)	26,411 (26.4)
25–29	1760 (34.8)	32,189 (33.3)	1841 (36.1)	36,521 (36.4)
30–34	789 (15.6)	13,728 (14.2)	1140 (22.4)	22,020 (22.0)
≥35	278 (5.4)	5663 (5.8)	825 (16.3)	15,125 (15.2)
Parental work-related physical activity				
Ever	1307 (25.7)	25,576 (26.5)	1246 (24.5)	23,160 (23.2)
Never	3760 (74.3)	71,112 (73.5)	3843 (75.5)	76,925 (76.8)
Year of birth[a]				
1965–1969	2808 (55.4)		2835 (55.7)	
1970–1974	1363 (26.9)		1353 (26.6)	
1975–1979	598 (11.8)		593 (11.7)	
1980–1984	225 (4.4)		227 (4.4)	
1985–1989	64 (1.3)		71 (1.4)	
1990–1994	9 (0.2)		10 (0.2)	
Age at diagnosis				
<25	39 (0.7)		40 (0.9)	
25–29	255 (5.0)		249 (4.9)	

(continued on next page)

Table 1 (*continued*)

	Women for whom maternal employment history were available		Women for whom paternal employment history were available	
	Cases N = 5067	Controls N = 96,688	Cases N = 5089	Controls N = 100,085
	(%)	(%)	(%)	(%)
30–34	732 (14.5)		745 (14.7)	
35–39	1234 (24.3)		1227 (24.2)	
40–44	1573 (31.0)		1563 (30.2)	
≥45	1234 (24.5)		1265 (24.9)	
ER status				
Negative	1289 (25.4)		1280 (26.1)	
Positive	2960 (58.4)		2965 (58.2)	
Missing	818 (22.2)		844 (15.7)	

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[a] Matching factor.

(Supplemental Table 2).

The fully adjusted results did only marginally differ from those with minimal adjustment (only results with minimum adjustment on ever employment are shown) (Table 2), and the fully adjusted results are thus presented in the remaining results section. Furthermore, the risk estimates obtained from our complete case analyses, which included family SES, did not significantly deviate from our main results (Supplemental Table 3).

Focusing on maternal employment, an adverse association between ever employment in "Horticulture" and breast cancer was indicated (OR = 1.33, 95% CI: 1.00–1.78). Preconceptional employment in all investigated agricultural industries was adversely associated with breast cancer. Furthermore, perinatal employment in "Horticulture" was indicated to elevate the risk (OR = 1.25, 95% CI: 0.76–2.06), while employment in all other agricultural industries in this time window was inversely associated with disease risk (Table 2). Focusing on paternal employment, risk estimates were decreased for most agricultural industries in the explored time windows, although an elevated risk was indicated for perinatal employment in "Horticulture" (OR = 1.20, 95% CI: 0.72–2.01) (Table 3).

Focusing on ER negative tumors, ever maternal employment across the various agricultural industries, except for "farming, crops", was associated with an elevated risk. A similar risk pattern was observed for preconceptional employment, including an elevated risk for "Agriculture, unspecified" (OR = 2.06, 95% CI: 1.17–3.60). Perinatal employment in "Horticulture" was indicated to increase the risk (OR = 2.48, 95% CI: 1.18–5.21). When focusing on ER positive tumors, ever maternal employment in "Horticulture" and "Farming, crops" showed a marginal increase in the risk. Except for "Agriculture, unspecified", the risk was indicated to be increased following preconceptional employment in all agricultural industries, and the risk was most elevated for "Horticulture" (OR = 1.79, 95% CI: 1.13–2.85). For perinatal employment, inverse associations were observed for all agricultural industries and ER positive tumors (Table 4).

Paternal employment in agricultural industries in the examined time windows was indicated to decrease or have no noteworthy effect on the risk of the explored hormonal subtypes, except for perinatal employment in "Horticulture" that was adversely associated with ER negative tumors (OR = 1.64, 95% CI: 0.71–3.80) (Table 5). Mutual adjustment for agricultural employment in the other parent did overall not alter the results (Supplemental Tables 4–5). The analysis exploring interactions between ever maternal and paternal employment in agriculture indicated that employment in most industries by both parents decreased the risk of breast cancer, except for parental employment in "horticulture" that tended to elevate the risk (OR = 1.85, 95% CI: 0.85–4.06) (Table 6).

4. Discussion

Findings from our study exploring the risk of breast cancer in daughters of agricultural workers indicated that paternal employment in most examined agricultural industries was associated with a decreased risk. However, our observations indicated that particularly maternal employment in "Horticulture" in the explored time windows increased

Table 2

Maternal agricultural employment: associations between work in different time windows and female breast cancer [OR = odds ratio; CI = confidence interval].

			Ever employment[a]					
DSE77	Industry[b]		Cases	Controls	OR[c]	95% CI	OR[d]	95% CI
11.101–209	Overall work in agriculture	No	4917	93,915	Ref.	–	Ref.	–
		Yes	150	2773	1.06	0.89–1.25	1.07	0.91–1.27
11.101	Agriculture, unspecified	No	5023	95,866	Ref.	–	Ref.	–
		Yes	44	822	1.02	0.75–1.39	1.04	0.76–1.41
11.102	Horticulture	No	5016	95,900	Ref.	–	Ref.	–
		Yes	51	788	1.28	0.96–1.71	1.33	1.00–1.78
11.111	Farming, crops	No	5018	95,789	Ref.	–	Ref.	–
		Yes	49	899	1.09	0.81.1.46	1.06	0.79–1.43

			Preconceptional employment[e]				Perinatal employment[f]			
			Cases	Controls	OR[d]	95% CI	Cases	Controls	OR[d]	95% CI
11.101–209	Overall work in agriculture	No	4961	94,844	Ref.	–	5023	95,759	Ref.	–
		Yes	106	1844	1.16	0.95–1.42	44	929	0.90	0.66–1.23
11.101	Agriculture, unspecified	No	5036	96,186	Ref.	–	5054	96,368	Ref.	–
		Yes	31	502	1.26	0.87–1.82	13	320	0.73	0.41–1.27
11.102	Horticulture	No	5033	96,177	Ref.	–	5050	96,411	Ref.	–
		Yes	34	511	1.37	0.96–1.95	17	277	1.25	0.76–2.06
11.111	Farming, crops	No	5030	96,035	Ref.	–	5055	96,442	Ref.	–
		Yes	37	653	1.13	0.81–1.59	12	246	0.90	0.50–1.61

[a] Up to one year following birth.

[b] Only industries and results with an appropriate number (N ≥ 5) of cases and controls are shown.

[c] Minimal adjusted model including the matching factor, i.e., year of birth.

[d] Fully adjusted model including the matching factor, birthplace, birth order, age at first birth, parity, family history of breast cancer, and employment in the listed agricultural industries in the study population of women; maternal age at birth and ever heavy occupational physical activity.

[e] Up to one year before birth.

[f] One year prior to birth up to one year following birth.

Table 3
Paternal agricultural employment: associations between work in different time windows and female breast cancer [OR = odds ratio; CI = confidence interval].

		Ever employment[a]											
DSE77	Industry[b]		Cases	Controls	OR[c]	95% CI	OR[d]	95% CI					
11.101–209	Overall work in agriculture	No	4789	93,045	Ref.	–	Ref.	–					
		Yes	300	7040	0.83	0.74–0.94	0.85	0.74–0.96					
11.101	Agriculture, unspecified	No	4983	97,183	Ref.	–	Ref.	–					
		Yes	106	2902	0.71	0.58–0.86	0.71	0.58–0.87					
11.102	Horticulture	No	5049	99,174	Ref.	–	Ref.	–					
		Yes	40	911	0.87	0.63–1.20	0.89	0.65–1.23					
11.111	Farming, crops	No	4979	97,931	Ref.	–	Ref.	–					
		Yes	110	2154	1.03	0.84–1.25	1.04	0.85–1.27					
11.112	Farming, livestock	No	5067	99,492	Ref.	–	Ref.	–					
		Yes	22	593	0.75	0.48–1.15	0.77	0.50–1.19					
11.201	Agricultural machinery stations	No	5050	99,174	Ref.	–	Ref.	–					
		Yes	39	911	0 .85	0.61–1.18	0.90	0.65–1.24					
		Preconceptional employment[e]								Perinatal employment[f]			
			Cases	Controls	OR[d]	95% CI				Cases	Controls	OR[d]	95% CI
11.101–209	Overall work in agriculture	No	4901	95,687	Ref.	–			No	4977	97,443	Ref.	–
		Yes	188	4398	0.89	0.78–1.02			Yes	112	2642	0.83	0.68–1.01
11.101	Agriculture, unspecified	No	5013	98,188	Ref.	–			No	5059	99,080	Ref.	–
		Yes	76	1897	0.81	0.64–1.02			Yes	30	1005	0.55	0.38–0.80
11.102	Horticulture	No	5065	99,433	Ref.	–			No	5073	99,826	Ref.	–
		Yes	24	652	0.76	0.51–1.15			Yes	16	259	1.20	0.72–2.01
11.111	Farming, crops	No	5015	98,691	Ref.	–			No	5053	99,325	Ref.	–
		Yes	74	1394	1.10	0.86–1.40			Yes	36	760	0 .93	0.66–1.33
11.112	Farming, livestock	No	5073	99,639	Ref.	–			No	5083	99,938	Ref.	–
		Yes	16	446	0.74	0.44–1.22			Yes	6	147	0.86	0.37–1.96
11.201	Agricultural machinery stations	No	5065	99,454	Ref.	–			No	5074	99,805	Ref.	–
		Yes	24	631	0.79	0.52–1.20			Yes	15	280	1.13	0.67–1.91

[a] Up to birth.
[b] Only industries and results with an appropriate number (N ≥ 5) of cases and controls are shown.
[c] Minimal adjusted model including the matching factor, i.e., year of birth of the index women.
[d] Fully adjusted model including the matching factor, birthplace, birth order, age at first birth, parity, family history of breast cancer, and employment in the listed agricultural industries in the study population of women; paternal age at birth and ever heavy occupational physical activity.
[e] Up to one year before birth.
[f] The year prior to birth.

the risk. Moreover, maternal preconceptional employment in "Horticulture" was indicated to elevate the risk of ER positive tumors while both maternal and paternal employment in the perinatal period was associated with an elevated risk of ER negative tumors.

Agricultural workers are generally considered to have a better health status than the general population, which may be attributed to healthier lifestyle habits relating to e.g., smoking, drinking, diet and physical activity (Thelin et al., 2009; Stiernström et al., 2001; Gallagher et al., 1984). Parental lifestyle factors may affect disease risk in offspring directly as evidence from animal studies suggest that maternal physical activity and diet affect breast cancer risk in offspring (Camarillo et al., 2014; Grassi et al., 2019) The risk may also be affected indirectly by adaption of parental healthy lifestyle habits (Pudrovska and Anikputa, 2012). This may in part explain the inverse associations observed between parental work in several examined agricultural sectors and breast cancer. However, some workplace hazards such as pesticide exposure may increase the risk of specific cancers in this working population, which may also manifest in next generations.

Our findings consistently indicating an association between parental horticultural work and breast cancer are biologically plausible as this agricultural industry has some distinctive characteristics regarding workplace hazards. In Denmark, the distribution of various sectors in horticulture is: ornamental plants (46%), open field vegetables (21%), greenhouse vegetables (14%), other plants (10%), and fruits and berries (8%), and in northern countries like Denmark much of the production across several sectors occurs in enclosed greenhouses (Gartneri, 2014). Unlike open field farming, greenhouses have confined physical indoor environments, limited space, and relatively hot and humid atmospheres. These indoor working conditions directly impact pesticide exposure levels, which are expected to be much higher compared to open fields (Amoatey et al., 2020; Tefera et al., 2019) The predominant types of applied pesticides in greenhouses include insecticides, fungicides, and growth regulators, with herbicides not usually being utilized (Brouwer et al., 1992a,b).

Pesticides are likely to distribute in the body, including in the breast, and they may also transfer transplacentally. Some pesticides that have been shown to cause mammary tumors or altering mammary gland development in experimental animal models, including the OP insecticides parathion and malathion (Cardona and Rudel, 2020), were widely applied in Danish agriculture during the study period (The Danish Environmental Protection Agency)). Evidence from some epidemiological studies also indicates that exposure to OP pesticides increases the risk of breast cancer (Yang et al., 2020). Studies examining the association between agriculture and breast cancer have overall presented inconsistent findings (Coogan et al., 1996; Katuwal et al., 2018; Sritharan et al., 2019; Settimi et al., 1999; Khalis et al., 2019; Brophy et al., 2006, 2012; Band et al., 2000; Mills and Yang, 2005; Pedersen and Hansen, 2022; Togawa et al., 2021), however, most studies have not differentiated between different work sectors. In support of our findings, results from the study by Band et al. examining different types of farming indicated an elevated breast cancer risk in women employed in fruit and other vegetable farming (OR = 3.11, 90% CI 1.24–7.81). For women ever employed in other vegetable farming, the risk was even greater (OR = 7.33, 90% CI 1.16–46.2) (Band et al., 2000).

Exposure to pesticides with endocrine-disrupting properties during pregnancy has been proposed to be particularly critical in relation to breast cancer (Nicolella and de Assis, 2022; Terry et al., 2019). During this vulnerable period, these chemicals can alter maternal hormone and growth factor levels, potentially affecting the normal development of the fetus' mammary glands (Terry et al., 2019). Other biological mechanisms may include epigenetic responses of offspring; evidence from

Table 4
Maternal agricultural employment: associations between work in different time windows and female breast cancer by estrogen receptor status [OR = odds ratio; CI = confidence interval].

	Industry (DSE) [a]		Estrogen receptor negative				Estrogen receptor positive			
			Cases	Controls	OR[b]	95% CI	Cases	Controls	OR[b]	95% CI
Ever employment[c]	Overall work in agriculture (11.101–209)	No	1241	23,173	Ref.	–	2882	53,835	Ref.	–
		Yes	48	750	1.22	0.90–1.65	78	1485	1.02	0.81–1.29
	Agriculture, unspecified (11.101)	No	1272	23,724	Ref.	–	2940	54,839	Ref.	–
		Yes	17	199	1.60	0.97–2.65	20	481	0.78	0.50–1.23
	Horticulture (11.102)	No	1272	23,702	Ref.	–	2935	54,920	Ref.	–
		Yes	17	221	1.54	0.93–2.55	25	400	1.28	0.85–1.93
	Farming, crops (11.111)	No	1278	23,673	Ref.	–	2931	54,850	Ref.	–
		Yes	11	250	0.79	0.43–1.46	29	470	1.20	0.82–1.76
Preconceptional employment[d]	Overall work in agriculture (11.101–209)	No	1256	23,400	Ref.	–	2902	54,386	Ref.	–
		Yes	33	523	1.23	0.86–1.77	58	934	1.22	0.93–1.61
	Agriculture, unspecified (11.101)	No	1275	23,724	Ref.	–	2947	55,042	Ref.	–
		Yes	14	134	2.06	1.17–3.60	13	481	0.91	0.52–1.60
	Horticulture (11.102)	No	1280	23,765	Ref.	–	2940	55,089	Ref.	–
		Yes	9	158	1.13	0.57–2.24	25	231	1.79	1.13–2.85
	Farming, crops (11.111)	No	1282	23,738	Ref.	–	2937	54,983	Ref.	–
		Yes	7	185	0.70	0.33–1.51	23	337	1.36	0.88–2.09
Perinatal employment[e]	Overall work in agriculture (11.101–209)	No	1274	23,696	Ref.	–	2940	54,769	Ref.	–
		Yes	15	227	1.17	0.69–1.98	20	551	0.69	0.44–1.08
	Agriculture, unspecified (11.101)	No	–	–	Ref.	–	2953	55,117	Ref.	–
		Yes	–	–	–	–	7	203	0.61	0.29–1.32
	Horticulture (11.102)	No	1281	23,860	Ref.	–	2955	55,151	Ref.	–
		Yes	8	63	2.48	1.18–5.21	5	169	0.60	0.24–1.48
	Farming, crops (11.111)	No	–	–	Ref.	–	2954	55,187	Ref.	–
		Yes	–	–	–	–	6	133	0.82	0.36–1.88

[a] Only industries and results with an appropriate number ($N \geq 5$) of cases and controls are shown.
[b] Fully adjusted model including the matching factor, i.e., year of birth, birthplace, birth order, age at first birth, parity, family history of breast cancer, and employment in the listed agricultural industries in the study population of women; Maternal age at birth and ever heavy occupational physical activity.
[c] Up to one year following birth.
[d] Up to one year before birth.
[e] One year prior to birth up to one year following birth.

examinations of DDT, including epidemiological studies, suggests that developmental exposure increases the risk of breast cancer in adulthood (Cohn et al., 2015, 2019; Chang et al., 2018). DDT has further been shown to cause changes in DNA methylation patterns in genes central for breast cancer (Wu et al., 2020). Parental exposure to pesticides prior to conception may also cause epigenetic alterations that are subsequently inherited; experimental animal studies have demonstrated that EDCs can lead to transgenerational transmission of breast cancer predisposition through both the male and female germlines (da Cruz et al., 2020).

For horticulture, we observed an increased risk of ER positive tumors following maternal preconceptual work and an elevated risk of ER negative tumors following parental perinatal work. Breast cancer is a heterogeneous disease and different risk factor profiles has been suggested for some subtypes. The etiology of particularly ER negative breast tumors is largely unknown and the biological mechanisms therefore remain unclear (Anderson et al., 2014b). A recent review (Rodgers et al., 2018) of chemical exposure and breast cancer included few examinations of pesticides and breast cancer by ER status; some findings indicated that DDT and similar chemicals used for insect control in the past were associated with only ER positive tumors. (White et al. (2013). However, major pesticides in horticulture post 1965 in Denmark are likely to have been different. Only few studies focusing on employment in agriculture have explored the risk of hormonal subtypes of breast cancer, including the study by Brophy et al. (2012) suggesting that farming had a stronger excess of ER negative breast tumors. Hence, our findings need to be confirmed in future breast cancer studies focusing on pesticides and agriculture, including information on susceptible time windows and breast cancer subtypes.

As our study is characterized by being explorative and several results were based on small numbers, our findings should be interpreted with caution. There are also some limitations, which we would like to acknowledge. Firstly, information on employment history from the Supplementary Pension Fund has some restrictions; this data does not include periods with self-employment, including self-employed farmers. Additionally, the Supplementary Pension Fund only holds employment information for individuals aged 18–66 years, and from 1978 onwards, workers aged 16–17 years were also included. This means that initial employment in agricultural industries, which usually begins at a young age, would not have been captured. Moreover, data on employment was only available from 1964 onwards, so parental employment in agriculture before this year would not have been included. For those born in subsequent years, ever and preconceptional employment could encompass a significantly broad span of their parents' work history, whereas these employment periods may have been misclassified for cases and controls born in 1965. Virtually all parents employed in agriculture in the perinatal period were also employed in the years following birth, and the effect of parental perinatal employment vs. potential take-home exposure to pesticides in early childhood could therefore not be evaluated. For especially mothers in our study, employment status in the perinatal time window may moreover have been misclassified due to job adjustment not involving usual exposures, absence, or parental leave. Hence, several issues may have caused misclassification of employment in explored time windows and thus have given rise to an attenuation of our results.

We also lacked information on several work characteristics, such as specific tasks and the use of protective equipment, especially in relation to pesticide application. We assumed uniform exposure at the industrial level, but future studies investigating parental agricultural work and the risk of breast cancer should incorporate detailed exposure assessments, including environmental sampling and biomonitoring specifically focusing on pesticide exposure.

In the present study, we used information on the legal guardians from DCRS, which in addition to biological relationships also includes adoptions. However, adoption status was not stated in our data. As adoption in Denmark is rare (Contreras et al., 2017), we did not expect that lack of this information would have influenced our findings.

Table 5
Paternal agricultural employment: associations between work in different time windows and female breast cancer by estrogen receptor status [OR = odds ratio; CI = confidence interval].

	Industry (DSE) [a]		Estrogen receptor negative				Estrogen receptor positive			
			Cases	Controls	OR[b]	95% CI	Cases	Controls	OR[b]	95% CI
Ever employment[c]	Overall work in agriculture (11.101–209)	No	1192	22,746	Ref.	–	2807	53,660	Ref.	–
		Yes	88	1902	0.90	0.72–1.13	158	3802	0.82	0.70–0.97
	Agriculture, unspecified (11.101)	No	1243	23,868	Ref.	–	2908	55,853	Ref.	–
		Yes	37	780	0.90	0.64–1.27	57	1609	0.68	0.52–0.89
	Horticulture (11.102)	No	1266	24,391	Ref.	–	2947	56,989	Ref.	–
		Yes	14	257	1.10	0.64–1.91	18	473	0.76	0.47–1.22
	Farming, crops (11.111)	No	1252	24,086	Ref.	–	2905	56,309	Ref.	–
		Yes	28	562	0.99	0.67–1.46	60	1153	1.04	0.79–1.35
	Farming, livestock (11.112)	No	1275	23,095	Ref.	–	2955	52,486	Ref.	–
		Yes	5	176	0.54	0.22–1.32	10	260	0.74	0.39–1.40
	Agricultural machinery stations (11.201)	No	1273	24,399	Ref.	–	2941	56,985	Ref.	–
		Yes	7	249	0.53	0.25–1.15	24	477	1.06	0.70–1.61
Preconceptional employment[d]	Overall work in agriculture (11.101–209)	No	1216	23,391	Ref.	–	2870	55,185	Ref.	–
		Yes	64	1257	1.02	0.78–1.33	95	2277	0.84	0.68–1.04
	Agriculture, unspecified (11.101)	No	1249	24,114	Ref.	–	2927	56,449	Ref.	–
		Yes	31	534	1.14	0.78–1.65	38	1013	0.74	0.53–1.03
	Horticulture (11.102)	No	1272	24,461	Ref.	–	2953	57,128	Ref.	–
		Yes	8	187	0.89	0.43–1.81	12	334	0.72	0.40–1.29
	Farming, crops (11.111)	No	1260	24,244	Ref.	–	2925	56,768	Ref.	–
		Yes	20	404	1.01	0.63–1.59	40	694	1.17	0.84–1.62
	Farming, livestock (11.112)	No	–	–	Ref.	–	2959	57,253	Ref.	–
		Yes	–	–	–	–	6	209	0.57	0.25–1.31
	Agricultural machinery stations (11.201)	No	1274	24,479	Ref.	–	2950	57,138	Ref.	–
		Yes	6	169	0.54	0.25–1.16	15	324	1.05	0.69–1.60
Perinatal employment[e]	Overall work in agriculture (11.101–209)	No	1256	24,003	Ref.	–	2902	55,937	Ref.	–
		Yes	24	645	0.70	0.46–1.06	63	1525	0.81	0.63–1.05
	Agriculture, unspecified (11.101)	No	1274	24,402	Ref.	–	2946	56,866	Ref.	–
		Yes	6	246	0.44	0.19–1.01	19	596	0.59	0.37–0.95
	Horticulture (11.102)	No	1274	24,578	Ref.	–	2959	57,323	Ref.	–
		Yes	6	70	1.64	0.71–3.80	6	139	0.84	0.37–1.91
	Farming, crops (11.111)	No	1272	24,490	Ref.	–	2945	57,003	Ref.	–
		Yes	8	158	0.96	0.46–1.96	20	459	0.84	0.53–1.33
	Agricultural machinery stations (11.201)	No	–	–	Ref.	–	2956	57,309	Ref.	–
		Yes	–	–	–	–	9	153	1.25	0.63–2.46

[a] Only industries and results with an appropriate number ($N \geq 5$) of cases and controls are shown.
[b] Fully adjusted model including the matching factor, i.e., year of birth, birthplace, birth order, age at first birth, parity, family history of breast cancer, and employment in the listed agricultural industries in the study population of women; paternal age at birth and ever occupational physical activity.
[c] Up to birth.
[d] Up to one year before birth.
[e] One year prior to birth up to birth.

Unfortunately, not all potential confounding factors were available in the present study, including important lifestyle factors such as alcohol consumption, use of oral contraceptives and hormone replacement therapy. However, family SES is associated with education, lifestyle preferences and SES in adulthood (Pudrovska and Anikputa, 2012), and we may therefore indirectly have accounted for lifestyle factors by adjusting for family SES in our complete case analyses, which did not alter our results considerably. Some evidence suggests that pesticide exposure may affect fertility (Vessa et al., 2022), and since low parity and higher age at birth in parents and potentially also in daughters may be due to low fecundity, we might have blurred possible associations by controlling for these potential intermediate variables. However, we analyzed data with and without controlling for these and this procedure did not give rise to any noteworthy differences in results. Concerning racial differences, all study participants were born in Denmark, and it is thus a fair assumption that the vast majority were Caucasian. Therefore, we do not expect that race would have confounded our results. Consequently, our results may only be generalizable to similar populations.

Pesticides are also found in the general environment, e.g., in agricultural products and groundwater, however, normally to a much lower extent than in the work environment. As a social disparity in toxicant burden from environmental chemicals most likely exists (Rajmohan et al., 2020), we may also have accounted for e.g., environmental pesticide exposure in our complete case analyses including family SES.

The strengths of our case-control study lie in its population-based design, the relatively large number of breast cancer cases diagnosed at an early stage of life, and the inclusion of information on hormonal subtypes. The data were retrieved from nationwide registries that contain high-quality information on employment and cancer. A notable aspect of our study was also the examination of both maternal and paternal employment during relevant time windows.

5. Conclusion

Findings from the study suggests that particularly paternal employment in most agricultural industries is inversely associated with the risk of breast cancer. However, parental employment in horticulture, which may involve high levels of pesticide exposure, was indicated to increase the risk of breast cancer. The association was observed to be strongest for maternal employment, and employment in different time windows was indicated to have distinct effects on the risk of breast cancer subtypes. These first findings need to be reproduced by forthcoming studies, including individual-level information on exposures and confounders relating to lifestyle.

Credit author Statement

JEP made significant contributions to the study by conceptualizing the research, conducting the analyses, interpreting the findings, and writing the manuscript. JH played a crucial role in designing the study, performing data cleaning and linkage, conducting the analyses, and providing critical revisions to the manuscript for important intellectual content. Both authors have reviewed and approved the final version of the manuscript for publication and take full responsibility for all aspects of the work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institution and ethics approval and informed consent.

The study is registry-based. No ethics approval for purely registry-based research is required in Denmark.

Disclaimer

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117374.

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