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Hormonal factors and pancreatic cancer risk in women: The Malmö Diet and Cancer Study

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The incidence of pancreatic cancer is leveling between sexes. Smoking, high age and heredity are established risk factors, but evidence regarding the influence of hormonal factors is unclear. In this study, we investigated the associations of reproductive factors, use of oral contraceptives (OC) and hormone replacement therapy (HRT) with pancreatic cancer risk in the Malmö Diet and Cancer Study, a prospective, population-based cohort encompassing 17,035 women. Up until 31 December 2015, 110 women were identified with incident pancreatic cancer through the Swedish Cancer Registry. Higher age at menarche was significantly associated with pancreatic cancer risk (age-adjusted [hazard ratio] HR = 1.17; 95% confidence interval [CI] 1.04–1.32, and fully adjusted HR = 1.17; 95% CI 1.04–1.32). Ever use of OC was not significantly associated with pancreatic cancer risk but ever use of HRT was significantly associated with a decreased risk of pancreatic cancer (age-adjusted HR = 0.47, 95% CI 0.23–0.97, and fully adjusted HR = 0.48, 95% CI 0.23–1.00), in particular use of estrogen-only regimen (age-adjusted HR = 0.21; 95% CI 0.05–0.87 and fully adjusted HR = 0.22; 95% CI 0.05–0.90). Age at menopause or first childbirth, parity and breastfeeding history were not significantly associated with pancreatic cancer risk. Collectively, these findings suggest a protective role of female hormones against pancreatic cancer. Further studies are needed, and potential modifying genetic factors and indirect hazardous effects of smoking should also be considered.

Cancer of the pancreas was recently reported by the World Health Organization to be the 11th most common cancer in women worldwide,[1] and due to its utterly poor prognosis, with a five-year overall survival of merely 5%,[1] it was the 7th most common cause of cancer related death.[2] In developed countries, the corresponding ranks were 8th and 4th,[2] respectively. In Sweden, The Board of Health and Welfare reported a total of 1,285 new cases of pancreatic cancer in 2015, 633 men and 652 women, with the highest incidence rate among individuals aged 70–74 years.[3] The distinct sex-related difference in incidence reported on a worldwide basis, with incidence rates being higher among men, thus no longer applies to Sweden. Tobacco smoking,[4–6] high age[4,7,8] and heredity[9,10] seem to be the only truly validated risk factors for pancreatic cancer. Several other risk factors have been investigated, and numerous studies claim a significant impact of diabetes,[11–13] pancreatitis,[14–16] alcohol[17–20] and body mass index (BMI)[13,21–23]; however, no consensus has yet been reached.

Numerous studies have investigated potential links between reproductive factors and pancreatic cancer risk, with conflicting results. Two studies found a significantly increased risk with earlier menarche,[24,25] whereas another study demonstrated an inverse correlation to age at menarche.[26] Several studies could not demonstrate a significant association between age at menarche and pancreatic cancer risk,[27–31] although the study related to the European Prospective Investigation into Cancer and Nutrition (EPIC) found a borderline significant increase in risk in individuals with age at menarche before 12 years of age.[31] Regarding age at menopause, studies demonstrating significant results are rare, and also contradictory, showing that a higher age at menopause is associated with either a decreased,[27] or an increased,[28] risk for pancreatic cancer.

In a study by Skinner *et al.*,[32] women with five or more children were shown to have a decreased risk of pancreatic

Key words: reproductive factors, hormone replacement therapy, oral contraceptives, pancreatic cancer risk

Abbreviations: BMI: body mass index; HRT: hormone replacement therapy; MDCS: Malmö Diet and Cancer Study; OC: oral contraceptives

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What's new?

Female hormones appear to protect against pancreatic cancer, at least in Sweden. Numerous studies have investigated the relationship between the two, but no clear picture has yet emerged. These authors used data from the Malmö Diet and Cancer study, looking for correlations between hormone levels and cancer risk. They found that a younger start to menstruation—indicating an earlier boost in estrogen—correlated with less chance of developing pancreatic cancer. Use of hormone replacement therapy, particularly estrogen-only therapy, significantly reduced risk among postmenopausal women. Breastfeeding, oral contraceptive use and parity did not appear to affect pancreatic cancer risk.

cancer compared to nulliparous women, with a significant risk reduction of 10% for each child born. Similar relationships have been confirmed in other studies.[33–36] The impact of age at first childbirth is less clear. While a few studies show an increased risk with higher age at first full-time pregnancy,[35,37] others show an increased risk with a lower age at first full-time pregnancy[38,39]; however, many claim no such correlation.[26,27,30] Concerning breastfeeding, the results are also limited, with most studies showing no correlation to pancreatic cancer risk.[29,30,32] Nevertheless, a Norwegian study describes breastfeeding as a potential protective factor, with a significantly decreased risk of pancreatic cancer for every 12 months of breastfeeding.[34]

Furthermore, the impact of hormone replacement therapy (HRT) has, to the best of our knowledge, only been shown to play a protective role against development of pancreatic cancer in one single study.[29] Regarding the use of oral contraceptives (OC) existing studies are few and show conflicting results, however, some demonstrate positive associations with risk of pancreatic cancer,[29,37] and some show inverse associations.[35]

In summary, the results regarding reproductive factors and hormone use in relation to pancreatic cancer risk are inconsistent. Therefore, the purpose of this study was to explore the associations of female hormone use and reproductive factors with risk of pancreatic cancer among all women in the Malmö Diet and Cancer Study (MDCS).

Methods

Study cohort

The study cohort consists of all women in the MDCS, a total of 17,035 participants, including all incident cases of pancreatic cancer up until December 31st 2015 ($n = 110$). MDCS is a population-based prospective cohort, part of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, encompassing a total of 28,098 participants (17,035 women and 11,063 men) recruited between 1991 and 1996, at age 44–73 years at baseline and has earlier been described in more detail.[40]

Pathology records were reviewed to confirm incident cases of pancreatic cancer reported from the Swedish Cancer register. All cases diagnosed at death were confirmed by autopsy and there were no death-certificate-only cases. Four participants were excluded from all analyses since no patient records were available and the diagnosis could neither be confirmed nor rejected. A flowchart of the study population is shown in Figure 1. The vital status of the participants at the study endpoint was retrieved from the National registration data by The Swedish Tax Agency (NAVET) and The National Board of Health and Welfare. Emigration dates were obtained from NAVET.

Ethics approval and consent to participate

The study was approved of by the Ethics committee of Lund University (ref nr 530/08 and 161/15). Written informed consent was obtained from each participant at study entry.

Statistical analysis

Cox proportional hazards analyses were applied to calculate hazard ratios (HR) and 95% confidence intervals (CI) for pancreatic cancer risk. Time on study was used as the underlying time scale, defined as time from baseline to diagnosis, emigration, death or end of follow-up 31 December 2015. Potential risk variables of interest, with particular reference to female physiology, were menstrual status at baseline, age at menarche, defined both as a continuous variable, and categorized into four groups ($\leq$11 years, $>$11–$\leq$14 years, $<$14–$\leq$16 years and $>$16 years), ever use of OC, nulliparity, number or children, age at first childbirth, breastfeeding, age at

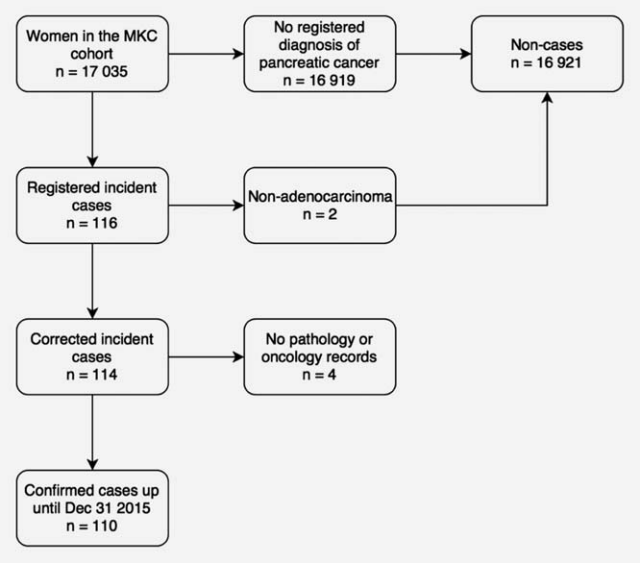

Figure 1. Flowchart of the cohort.

Table 1. Summary of the distribution of risk factors among pancreatic cancer cases and noncases

MKC women ($n = 17,031$)				
Characteristics	**Entire cohort**	**Noncases**	**Cases**	***p* value**
n (%)	17,031	16,921 (99.4)	110 (0.6)	
Age at baseline (years)				
Median	56.7	56.7	61.0	<0.001
Range	44.5–73.6	44.5–73.6	45.8–73.0	
Std. deviation	7.88	7.88	7.50	
Menstrual status at baseline				
Pre	4452 (26.1)	4430 (26.2)	22 (20.0)	0.141
Peri + post	12579 (73.9)	12491 (73.8)	88 (80.0)	
Age at menarche (years)				
Median	14.0	14.0	14.0	0.042
Range	8.0–26.0	8.0–26.0	10.0–22.0	
Std. deviation	1.49	1.48	1.89	
Missing	125	125	0	
Age at menarche (categories)				
≤11 years	1138 (6.7)	1131 (6.7)	7 (6.4)	0.021
>11–≤14 years	11598 (68.1)	11531 (68.1)	67 (60.9)	
>14–≤16 years	3615 (21.2)	3588 (21.2)	27 (24.5)	
>16 years	555 (3.3)	546 (3.2)	9 (8.2)	
Missing	125 (0.7)	125 (0.7)	0	
Ever use of oral contraceptives				
Never	8664 (50.9)	8593 (50.8)	71 (64.5)	0.004
Ever	8351 (49.0)	8312 (49.1)	39 (35.5)	
Missing	16 (0.1)	16 (0.1)	0	
Ever use of oral contraceptives 1960–1980 or later				
Never	8664 (50.9)	8593 (50.8)	71 (64.5)	0.004
1980	238 (1.4)	237 (1.4)	1 (0.9)	
1960–1980	7873 (46.2)	7837 (46.3)	36 (32.7)	
Missing	256 (1.5)	254 (1.5)	2 (1.8)	
Ever use of oral contraceptives 1960–1970 or later				
Never	8664 (50.9)	8593 (50.8)	71 (64.5)	0.004
1970	1940 (11.4)	1930 (11.4)	10 (9.1)	
1960–1970	6171 (36.2)	6144 (36.3)	27 (24.5)	
Missing	256 (1.5)	254 (1.5)	2 (1.8)	
Nulliparity				
No	14557 (85.5)	14463 (85.5)	94 (85.5)	0.980
Yes	2184 (12.8)	2170 (12.8)	14 (12.7)	
Missing	290 (1.7)	288 (1.7)	2 (1.8)	
Age at first child birth (years)				
Median	24.0	24.0	23.0	0.087
Range	11.0–51.0	11.0–51.0	15.0–38.0	
Std. deviation	4.66	4.66	4.50	
Missing	2486	2470	16	
Parity (number of children)				
Zero	2184 (12.8)	2170 (12.8)	14 (12.7)	0.991

Table 1. Summary of the distribution of risk factors among pancreatic cancer cases and noncases (Continued)

MKC women ($n = 17,031$)				
Characteristics	**Entire cohort**	**Noncases**	**Cases**	***p* value**
One	3640 (21.4)	3616 (21.4)	24 (21.8)	
Two	6989 (41.0)	6944 (41.0)	45 (40.9)	
Three	2812 (16.5)	2795 (16.5)	17 (15.5)	
Four or more	1116 (6.6)	1108 (6.5)	8 (7.3)	
Missing	290 (1.7)	288 (1.7)	2 (1.8)	
Total time breastfeeding (months)				
Median	8.0	8.0	9.0	0.854
Range	1.0–96.0	1.0–96.0	1.0–41.0	
Std. deviation	7.77	7.78	7.18	
Missing	3755	3734	21	
Total time breastfeeding (categories)				
<4 months	2419 (14.2)	2405 (14.2)	14 (12.7)	0.966
≥4–<8 months	3848 (22.6)	3821 (22.6)	27 (24.5)	
≥8–<13 months	3607 (21.2)	3579 (21.2)	28 (25.5)	
≥13 months	3402 (20.0)	3382 (20.0)	20 (18.2)	
Missing	3755 (22.0)	3734 (22.1)	21 (19.1)	
Age at menopause (years)				
Median	50.0	50.0	50.0	0.724
Range	28.0–67.0	28.0–67.0	34.0–58.0	
Std. deviation	4.83	4.83	4.87	
Missing	1413	1408	5	
Years of menstruation				
Median	36.0	36.0	35.0	0.518
Range	10.0–54.0	10.0–54.0	20.0–46.0	
Std. deviation	4.98	4.98	5.08	
Missing	1473	1468	5	
Hormone replacement therapy				
Never	10170 (80.8)	10090 (80.8)	80 (90.9)	0.018
Ever	2368 (18.8)	2360 (18.9)	8 (9.1)	
Missing	41 (0.3)	41 (0.3)	0	
HRT: Estrogen only				
Never	11320 (90.0)	11234 (89.9)	86 (97.7)	0.018
Ever	1218 (9.7)	1216 (9.7)	2 (2.3)	
Missing	41 (0.3)	41 (0.3)	0	
HRT: Gestagen only				
Never	12284 (97.7)	11298 (97.7)	86 (97.7)	0.869
Ever	254 (2.0)	252 (2.0)	2 (2.3)	
Missing	41 (0.3)	41 (0.3)	0	
HRT: Gestagen + estrogen				
Never	11406 (90.7)	11324 (90.7)	82 (93.2)	0.468
Ever	1132 (9.0)	1126 (9.0)	6 (6.8)	
Missing	41 (0.3)	41 (0.3)	0	
Bilateral oophorectomy				
No	16777 (98.5)	16670 (98.5)	107 (97.3)	0.283

Table 1. Summary of the distribution of risk factors among pancreatic cancer cases and noncases (Continued)

MKC women ($n = 17,031$)				
Characteristics	Entire cohort	Noncases	Cases	p value
Yes	254 (1.5)	251 (1.5)	3 (2.7)	
Womb and/or one or both ovaries removed				
No	6138 (36.0)	6107 (36.1)	31 (28.2)	0.058
Yes	1134 (6.7)	1123 (6.6)	11 (10.0)	
Missing	9759 (57.3)	9691 (57.3)	68 (61.8)	

menopause, total number of years with menstruation periods, ever use of HRT (estrogen, gestagen or combined), hysterectomy and/or oophorectomy. Menstrual status at baseline was recorded as pre-, peri- or post-menopausal, based on information from the questionnaire at baseline, hospital records and previous surgery, with peri- and postmenopausal women merged into the same category in the analyses of this study, further on referred to as postmenopausal. Analyses of HRT were performed only among postmenopausal women.

As modern contraceptives contain considerably lower hormone doses than earlier generations of OC, ever users of OC were also divided into groups based on which year they started using OC for analyses concerning the potential difference in impact on risk of pancreatic cancer.

Analyses were computed as age-adjusted and multivariable, adjusted for age, smoking, alcohol consumption and BMI. The confounders were chosen on the basis of being proposed or established risk factors for pancreatic cancer, or factors known to influence estrogen levels. Age was recorded as a continuous variable, and all analyses were also run with attained age as time-scale, and with and without adjusting for calendar year effects, with year of birth categorized into 5-year intervals.[41] Alcohol consumption was defined as grams per day, while tobacco smoking was recorded as never, former, occasional or regular smoking. Concerning environmental exposure to tobacco smoke (ETS), exposure during childhood was denoted as yes or no, exposure at work and at home, respectively, as no, <10 years, 10–20 years or >20 years. BMI was defined as a continuous variable.

The proportional hazard (PH) assumption was tested using Cox regression with a time-dependent covariate analysis and log-minus-log plots, and was considered to be satisfied when the factor $\times$ time interaction was nonsignificant and graphical assessment of log-minus-log plots displayed nonintersecting vectors.

All statistical analyses were computed using IBM SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two sided with p values <0.05 considered significant.

Results

Characteristics at baseline in cases and noncases

A description of baseline characteristics among incident pancreatic cancer cases and noncases is shown in Table 1. Age at baseline was significantly higher among cases compared with noncases ($p < 0.001$). Furthermore, age at menarche, both as a continuous and a categorized variable, was significantly higher among cases compared with noncases ($p = 0.042$ and $p = 0.021$ respectively). Cases were using OC to a lesser extent compared with noncases ($p = 0.004$), and were also less frequently users of HRT ($p = 0.018$). HRT use specified as estrogen substitution only was also more common among noncases compared with cases ($p = 0.018$).

Pancreatic cancer risk in relation to menstrual history, parity, breast-feeding and history of hysterectomy and/or oophorectomy

The time-dependent covariate was nonsignificant for all investigated factors, and therefore the factor $\times$ time interaction term was dropped from the model. The proportional hazard assumption was also considered to be satisfied with graphical evaluation using log-minus-log plots (data not shown).

The associations of age, smoking habits, alcohol consumption, BMI and educational level with pancreatic cancer risk with the updated follow-up time until December 31st 2015 are shown in Table 2. In line with our previous study,[42] not only regular, but also occasional smoking as well as exposure at work for >20 years were significantly associated with pancreatic cancer risk. Furthermore, a higher age at baseline was a significant risk factor. Alcohol consumption, educational level and BMI were not significantly associated with pancreatic cancer risk.

Pancreatic cancer risk in relation to menstrual history, parity, breastfeeding and history of hystero-oophorectomy is shown in Table 3, including analyses adjusted for age and adjusted for age, smoking, alcohol consumption and BMI.

Pancreatic cancer risk was shown to be significantly higher in women with a higher age at menarche in the age-adjusted analysis (HR = 1.17; 95% CI 1.04–1.32), and when adjusted for age, smoking, alcohol consumption and BMI (HR = 1.17; 95% CI 1.04–1.32). Adjusting for total years of menstruation in the latter model did not significantly alter this correlation ($p = 0.041$). The relationship between age at menarche and pancreatic cancer risk using categorized variables rendered a borderline significant trend toward an increased risk with higher categories of age at menarche in

Table 2. Risk of incident pancreatic cancer in relation to age, education, smoking, alcohol consumption and BMI

	Age-adjusted		Adjusted for age, smoking, alcohol consumption and BMI	
MKC women ($n = 17,031$)	***n***	**HR**	***n***	**HR**
		Age at baseline		
Years	17031	1.05 (1.03–1.08)	17031	1.07 (1.04–1.09)
p value		<0.001		< 0.001
		Educational level		
O-level collage	11861	1.00	11836	1.00
A-level collage	1182	0.42 (0.13–1.33)	1180	0.42 (0.13–1.33)
University	3945	0.84 (0.51–1.38)	3941	0.87 (0.52–1.44)
p trend		0.358		0.441
		Smoking		
Never	7525	1.00	7517	1.00
Former	4724	1.33 (0.80–2.21)	4714	1.31 (0.79–2.17)
Occasional	729	3.01 (1.39–6.52)	728	2.99 (1.38–6.49)
Regularly	4047	2.76 (1.74–4.36)	4040	2.78 (1.75–4.42)
p trend		< 0.001		< 0.001
		Environmental smoking at work		
Never	8465	1.00	8443	1.00
For <10 years	2204	1.13 (0.60–2.15)	2201	1.19 (0.63–2.26)
For 10–20 years	2112	1.25 (0.67–2.33)	2111	1.15 (0.62–2.14)
For >20 years	2514	2.30 (1.43–3.70)	2511	1.95 (1.20–3.17)
p trend		0.002		0.013
		Environmental smoking at home		
Never	7915	1.00	7896	1.00
For <10 years	1854	0.86 (0.43–1.81)	1853	0.82 (0.40–1.67)
For 10–20 years	2025	0.92 (0.48–1.77)	2024	0.81 (0.42–1.57)
For >20 years	3443	1.40 (0.88–2.23)	3435	1.15 (0.72–1.84)
p trend		0.213		0.683
		Environmental smoking during childhood		
No	5336	1.00	5324	1.00
Yes	9940	1.16 (0.76–1.78)	9924	1.10 (0.72–1.69)
p value		0.488		0.665
		Alcohol		
grams/day	17031	1.01 (0.99–1.03)	16999	1.01 (0.99–1.03)
p value		0.252		0.427
		Body Mass Index		
kg/m^2	17005	1.01 (0.97–1.05)	16999	1.02 (0.98–1.07)
p value		0.699		0.345

the age-adjusted as well as in the fully adjusted analysis ($p_{trend} = 0.055$ and 0.050, respectively), however, when adjusting also for total years of menstruation this association was no longer significant ($p_{trend} = 0.139$).

Menstrual status at baseline, age at menopause and total years of menstruation were not significantly associated with pancreatic cancer risk, and, apart from a borderline significant relationship between age at first childbirth and pancreatic cancer risk in the age-adjusted analysis (HR = 0.96; 95% CI 0.91–1.00), neither were parity, nulliparity, age at first childbirth nor breastfeeding.

Having a history of resection of the uterus and/or one or both ovaries was not significantly associated with pancreatic cancer risk.

Table 3. Risk of incident pancreatic cancer in relation to reproductive factors and history of hystero-oophorectomy

	Age-adjusted		Adjusted for age, smoking, alcohol consumption and BMI	
MKC women ($n = 17,031$)	*n*	HR	*n*	HR
Menstrual status at baseline				
Pre	4452	1.00	4448	1.00
Peri + post	12579	0.72 (0.39–1.34)	12551	0.66 (0.36–1.22)
p value		0.297		0.184
Age at menarche				
Years	16906	1.17 (1.04–1.32)	16877	1.17 (1.04–1.32)
p value		0.009		0.008
Age at menarche (categories)				
≤11 years	1138	1.00	1138	1.00
>11–≤14 years	11598	0.86 (0.39–1.87)	11577	0.92 (0.42–2.01)
>14–≤16 years	3615	1.04 (0.45–2.40)	3608	1.11 (0.48–2.58)
>16 years	555	2.27 (0.84–6.12)	554	2.38 (0.88–6.43)
p trend		0.055		0.050
Nulliparity				
No	14557	1.00	14537	1.00
Yes	2184	1.01 (0.57–1.77)	2174	1.03 (0.59–1.81)
p value		0.980		0.919
Age at first child birth				
Years	14545	0.96 (0.91–1.00)	14526	0.97 (0.92–1.01)
p value		0.054		0.161
Parity (number of children)				
Zero	2184	1.00	2174	1.00
One	3640	0.99 (0.51–1.92)	3635	0.95 (0.49–1.83)
Two	6989	1.02 (0.56–1.86)	6980	1.03 (0.56–1.88)
Three	2812	0.92 (0.45–1.86)	2809	0.89 (0.44–1.81)
Four or more	1116	1.03 (0.43–2.46)	1113	0.94 (0.39–2.25)
p trend		0.931		0.839
Total time breastfeeding				
Months	13276	0.99 (0.96–1.02)	13257	1.00 (0.97–1.02)
p value		0.585		0.715
Total time breastfeeding (categories)				
<4 months	2419	1.00	2415	1.00
≥4–<8 months	3848	1.17 (0.61–2.23)	3841	1.22 (0.64–2.32)
≥8–<13 months	3607	1.23 (0.65–2.34)	3605	1.31 (0.69–2.50)
≥13 months	3402	0.89 (0.45–1.76)	3396	0.96 (0.48–1.91)
p trend		0.674		0.864
Age at menopause				
Years	11166	0.98 (0.94–1.03)	11139	0.99 (0.95–1.04)
p value		0.494		0.661
Years of menstruation				
Years	11106	0.97 (0.93–1.01)	11081	0.98 (0.94–1.02)
p value		0.176		0.261

Table 3. Risk of incident pancreatic cancer in relation to reproductive factors and history of hystero-oophorectomy (Continued)

	Age-adjusted		Adjusted for age, smoking, alcohol consumption and BMI	
MKC women ($n = 17,031$)	*n*	HR	*n*	HR
Bilateral oophorectomy				
No	16777	1.00	16745	1.00
Yes	254	1.75 (0.56–5.51)	254	1.70 (0.54–5.35)
p value		0.340		0.368
Womb and/or one or both ovaries removed				
No	6138	1.00	6126	1.00
Yes	1134	1.76 (0.88–3.52)	1134	1.73 (0.86–3.45)
p value		0.110		0.124

Similar findings were seen for all factors when applying attained age as time-scale and when adjusting for calendar year effects (data not shown).

Pancreatic cancer risk in relation to use of oral contraceptives and use of hormonal replacement therapy

Pancreatic cancer risk in relation to OC and HRT use is shown in Table 4, including analyses adjusted for age and adjusted for age, smoking, alcohol consumption and BMI.

Ever use of OC was not significantly associated with risk of pancreatic cancer, neither overall nor when comparing earlier versus later regimens.

Ever use of HRT, any type of regimen, was significantly associated with a reduced risk of pancreatic cancer in the age-adjusted analysis (HR = 0.47; 95% CI 0.23–0.97), as well as in the fully adjusted analysis (HR = 0.48; 95% CI 0.23–1.00). Among women ever using estrogen only substitution, there was a decreased risk in both the age-adjusted and fully adjusted analyses (HR = 0.21; 95% CI 0.05–0.87 and HR = 0.22; 95% CI 0.05–0.90, respectively), whereas gestagen only or combined estrogen and gestagen substitution were not significantly associated with pancreatic cancer risk.

Similar findings were seen for all factors when applying attained age as time-scale and when adjusting for calendar year effects (data not shown).

Discussion

Collectively, the findings in this study indicate a protective effect of female hormones against pancreatic cancer in women.

A lower age at menarche, hence an earlier burst of estrogen levels,[43] was associated with a significantly decreased risk, whereas a higher age at menopause was not a significant protective factor. Moreover, there was no significant relationship between the total number of menstruating years and pancreatic cancer risk, and the increased risk with older age at menarche remained significant after adjusting for years of menstruation. These findings indicate that pancreatic cancer may indeed develop many years before the debut of symptoms.[44]

Of note, ever use of OC was not significantly associated risk of pancreatic cancer, but HRT use was shown to be associated with a significantly reduced risk in postmenopausal women, in particular when specifying the use to estrogen only. These findings additionally support that estrogen may have a protective effect against developing pancreatic cancer. Numerous studies have been conducted in this field[27,28,31,32,35,45]; however, very few have been able to present a significant protective effect of HRT on pancreatic cancer risk,[29] and further confirmatory studies are therefore warranted.

Breastfeeding had no impact on pancreatic cancer risk, which is in accordance with most previous studies,[29,30,32] and therefore, further strengthens the absence of such a relationship. Similarly, in line with several previous studies,[26,27,30] neither did age at first child birth correlate significantly with risk; however, there was a borderline significantly decreased risk with increasing age in the age-adjusted analysis, a correlation more markedly observed in a few former studies.[38,39] In contrast, other studies have shown an increased risk among women with a higher age at first childbirth,[35,37] and, taken together, this incoherence suggests an absence of a strong relationship between age at first childbirth and pancreatic cancer risk.

The lack of a correlation between parity and pancreatic cancer risk is in conflict with the results from previous studies.[32–34] The reason for this discrepancy is not clear, but, of note, those studies encompassed a larger number of noncases and cases than this study, in which some of the subgroups regarding parity were quite small.

Several decades ago, a couple of short articles concerning the relationship between estrogen and pancreatic cancer risk were published in *The Lancet*,[46,47] in light of the high male–female incidence rates seen in younger, but not in older patients. Accordingly, this was pondered to reflect the lowering levels of estrogen in elderly women, hence declaring estrogen a protective factor. However, due to the straggling results from studies conducted ever since, the relationship seems to be more multifaceted and complex, involving interactions between heredity, environmental exposures, body

Table 4. Risk of incident pancreatic cancer in relation to use of oral contraceptives and hormone replacement therapy

	Age-adjusted		Adjusted for age, smoking, alcohol consumption and BMI	
MKC women ($n = 17,031$)	*n*	HR	*n*	HR
Ever use of oral contraceptives				
Never	8664	1.00	8641	1.00
Ever	8351	0.73 (0.47–1.13)	8343	0.68 (0.44–1.06)
p value		0.156		0.091
Ever use of oral contraceptives 1960–1980 or later				
Never	8664	1.00	8641	1.00
1980	238	0.74 (0.10–5.42)	238	0.80 (0.11–5.90)
1960–1980	7873	0.72 (0.46–1.13)	7865	0.68 (0.43–1.07)
p trend		0.156		0.092
Ever use of oral contraceptives 1960–1970 or later				
Never	8664	1.00	8641	1.00
1970	1940	0.84 (0.42–1.69)	1940	0.84 (0.42–1.69)
1960–1970	6171	0.69 (0.43–1.12)	6163	0.64 (0.39–1.04)
p trend		0.131		0.071
Hormone replacement therapy (HRT)				
Never	10170	1.00	10146	1.00
Ever	2368	0.47 (0.23–0.97)	2364	0.48 (0.23–1.00)
p value		0.042		0.049
HRT: Estrogen only				
Never	11320	1.00	11295	1.00
Ever	1218	0.21 (0.05–0.87)	1215	0.22 (0.05–0.90)
p value		0.031		0.035
HRT: Gestagen only				
Never	12284	1.00	12257	1.00
Ever	254	1.41 (0.34–5.76)	253	1.43 (0.35–5.86)
p value		0.635		0.620
HRT: Gestagen + estrogen				
Never	11406	1.00	11379	1.00
Ever	1132	0.89 (0.39–2.07)	1131	0.91 (0.39–2.11)
p value		0.793		0.817

constitution, menstrual and reproductive factors, comorbidity and use of pharmaceutical substances.

As mentioned, several studies present results showing an increased risk of pancreatic cancer with increasing BMI,[13,21–23] which has not been observed in the MDCS, neither in men nor in women.[42] Still, adipose tissue is also known to produce estrogens, thus suggesting it may play a protective role as well. For these noncoherent facts not to interfere with our results, we chose to adjust for BMI in the fully adjusted model.

Smoking is the strongest risk factor for pancreatic cancer yet identified, and several studies have demonstrated a link between tobacco smoking and diminished levels of estrogen.[48–50] Estrogen receptors have been found in the normal pancreas, as well as in neoplastic pancreatic tissue, and are thus believed to have an important influence on pancreatic tissue growth and perhaps also on pancreatic carcinogenesis.[51–53]

While this study does not provide any further mechanistic insight into a potential protective effect of estrogen on pancreatic cancer risk, some aspects are noteworthy: It is plausible to assume that the increased smoking rate among women is the most significant factor underlying the levelling incidence between sexes, independent of the potential effects of tobacco smoke on estrogen levels. It is however noteworthy that findings in our previous study,[42] and further confirmed herein after the update in 2015, indicate that women may be more susceptible to the harmful effects of tobacco smoking than men, as not only regular smoking, but also occasional

smoking and environmental smoking at work were associated with pancreatic cancer risk. Speculatively, such an increased susceptibility may be explained by an inhibitory effect of smoking on the potential protective effects of estrogen. Adding to this, the decreasing use of HRT may also influence pancreatic cancer risk in women, which should be taken into consideration in future epidemiological studies.

Compared with several of the studies referred to herein, being case–control studies, our results are based upon a population-based prospective cohort, with all noncases being controls. While this renders a smaller number of cases compared to the majority of reported case–control studies, the proportion of female participants in the MDCS is still rather high. Of note, the incidence of pancreatic cancer among women is 0.6% in the MDCS up until 2015, which is similar to the incidence of 0.7% for women in developed countries from 0 to 74 years reported by Torre *et al.*[2] However, given that the women in the MDCS are followed from 45 years of age, hence during a period of time with an increasing incidence of pancreatic cancer, the number of cases appears to be in line with the expected.

It should also be pointed out that although the MDCS is part of the EPIC cohort, results are not directly comparable. Participants in the EPIC cohort have been recruited through 23 centers in 10 European countries, and while the majority of the cohorts represent the general population, others have recruited participants among, for example, blood donors, vegetarian volunteers or women attending breast cancer screening programs.[54]

A limitation to the study is that although the majority of the investigative variables have few missing values, some have a larger number of missing values, thus limiting the reliability of these particular analyses. Another limitation is the possibility of type 1 errors due to the extensive number of analyses. Furthermore, there is no information on the total number of pregnancies, including spontaneous or induced abortions, which may also be important factors to consider. Moreover, as for parity, there is no information on whether the women have given birth to additional children after study entry. However, with the youngest woman entering the study at age 44, this in unlikely to interfere with our results. Moreover, due to the design of the study, with information on exposure only recorded at study entry, there is a lack of updated exposure information during the study period.

Conclusion

The results from this study provide further evidence of a protective role of estrogen against the development of pancreatic cancer in women. The strongest pieces of evidence in support of this claim are the significantly decreased risk among ever users of estrogen based HRT and the significantly increased risk among women with a higher age at menarche. Adding to this, the indisputable association between cigarette smoking and pancreatic cancer risk has previously been shown to be even stronger among women in the herein examined cohort. In light of the levelling incidence between sexes, these findings call for further studies to elucidate the influence of sex hormones on pancreatic carcinogenesis, wherein potential modifying effects of genotype and indirect hazardous effects of smoking should also be considered.

Authors' Contributions

G.A. collected clinical data, performed the statistical analyses and drafted the manuscript. S.B. assisted with the statistical analyses and helped drafting the manuscript. K.J. conceived the study, assisted with the statistical analyses and helped drafting the manuscript. All authors read and approved the final manuscript.

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