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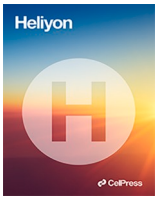

Research article

Hormone replacement therapy and risk of pancreatic cancer in postmenopausal women: Evidence from the US National Inpatient Sample 2008–2018

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ABSTRACT

Background: Pancreatic cancer is a serious, usually fatal disease and one of the most aggressive malignancies. Research into whether hormone replacement therapy (HRT) might protect against pancreatic cancer has yielded mixed results. This study aimed to investigate the potential association between HRT and the risk of pancreatic cancer in postmenopausal women.
Methods: This population-based, retrospective study extracted data from the US National Inpatient Sample (NIS) 2008–2018. Hospitalized females aged ≥55 years were eligible for inclusion. Associations between HRT, other study variables, and pancreatic cancer diagnosis were determined using univariate and multivariable regression analyses.
Results: After 1:4 matching by age, data of postmenopausal women with (n = 35,309) and without (n = 141,236) HRT were included in the analysis. The mean age was 73.4 years. Multivariable analyses showed that women with HRT had significantly decreased odds of pancreatic cancer (adjusted OR [aOR], 0.69, 95 % CI: 0.53–0.90). Compared to patients without HRT, patients with HRT in the 55-64-year-old group (aOR 0.48, 95 % CI: 0.32–0.74), 65-74-year-old group (aOR 0.49, 95 % CI: 0.34–0.71), non-hypertensive group (aOR 0.55, 95 % CI: 0.38–0.79), and non-hyperlipidemia group (aOR 0.59, 95 % CI: 0.42–0.82) had significantly decreased odds of pancreatic cancer.
Conclusions: In US postmenopausal women, HRT is associated with a reduced risk of pancreatic cancer, especially those aged 55–74 year. Further study is needed to clarify the mechanisms underlying the associations.

1. Introduction

Pancreatic cancer is a serious, usually fatal disease and one of the most aggressive malignancies. It is the tenth cause of cancer incidence and the third leading cause of cancer deaths in the US, with a 5-year survival rate of 12.5 % [1]. Diagnoses of pancreatic

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cancer are commonly made in the late stage. The prognosis of pancreatic cancer is the least favorable of all malignancies [2,3]. The 5-year overall survival rate of patients with pancreatic cancer is only about 10 %, with little difference between high-income countries and low- and middle-income countries [4]. The majority (90 %) of pancreatic neoplasms are pancreatic ductal adenocarcinomas (PDAC), with acinar carcinoma, pancreaticoblastoma, and neuroendocrine tumors as the remaining subtypes [5–7]. Over the past 25 years, the worldwide impact of pancreatic cancer has doubled, with both incidence and mortality rates rising in connection with an aging population [8–10]. The Surveillance, Epidemiology, and End Results Program indicates that around 57,600 cases of pancreatic cancer were diagnosed in 2020, leading to 47,050 fatalities [11]. Despite advances in understanding the underlying risk factors leading to pancreatic cancer, its incidence is projected to continue to increase, reaching an estimated 355,317 new cases by 2040 [12]. Surgery stands as the fundamental treatment approach for pancreatic cancer, however, upon diagnosis, upwards of 80 % of patients present with disease stages that are beyond the scope of surgical removal [13]. The recognized risk factors for pancreatic cancer encompass diabetes, aging, tobacco use, obesity, and genetic predispositions [14–16].

Sex steroid hormones, including estrogens, progesterone, and androgens, exert their influences by attaching to designated receptors, with the impact differing across various tissues and cell types. In the normal exocrine pancreas, two types of estrogen receptors (ESR1, also known as Erα, and ESR2, or Erβ) are present. Studies in animal models have demonstrated that estrogens can suppress the development of both pre-neoplastic lesions in the pancreas and pancreatic cancer [17,18]. Current epidemiological research indicates a gender disparity in pancreatic cancer incidence, with women experiencing lower rates than men across various age groups [19,20]. It is also recognized that hormone replacement therapy (HRT), commonly prescribed for postmenopausal women, can reduce insulin levels, a known risk factor for PDAC [21]. However, previous studies have reported mixed associations between HRT use and the risk of developing PDAC, with some indicating an increased risk [22,23], others suggesting a decreased risk [24,25], and several studies finding no association at all [24,26,27]. This warrants the need for further in-depth investigation.

Following this context, therefore, the present study sought to evaluate the relationship between pancreatic cancer and HRT use in postmenopausal women, using data from a a large nationally representative cohort of the US.

2. Methods

2.1. Data source

This population-based, retrospective observational study extracted all data from the US National Inpatient Sample (NIS) database, which is the largest all-payer, continuous inpatient care database in the US, including about 8 million hospital stays each year [28]. The database is administered by the Healthcare Cost and Utilization Project (HCUP) of the US National Institutes of Health (NIH). The patient data consist of primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographics, projected payment source, hospital stay duration, and hospital characteristics (i.e., bed size/location/teaching status/hospital area). The continuously updated, annual NIS contains patient information from around 1050 hospitals in 44 states, representing a stratified sample of 20 % of US community hospitals as defined by the American Hospital Association. Dataset details are available at: https://hcup-us.ahrq.gov/nisoverview.jsp.

2.2. Ethics statement

All data were obtained through request to the Online HCUP Central Distributor (available at: https://www.distributor.hcup-us.ahrq.gov/), which administers the database. This study conforms to the NIS data-use agreement (certificate # HCUP-359L52GVU). Because this study analyzed data from the NIS database, patients and the public were not involved directly. The study protocol was submitted to the Institutional Review Board of Renji Hospital, which exempted the study from further approval. Since all data in the NIS database are de-identified, the requirement for informed consent was also waived.

2.3. Study population

Data of all hospitalized female patients aged ≧ 55 years were extracted from the NIS database from 2008 to 2018. All diagnoses and procedures during hospitalizations were identified using the International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM, ICD-10-CM) codes. Women who were receiving HRT were confirmed by ICD 9-CM code V07.4 and ICD 10-CM code Z79.890, where pancreatic cancers were confirmed by ICD 9-CM code 157 and ICD 10-CM code C25. For further comparisons, women were further categorized into two groups according to with and without HRT use.

2.4. Covariates

Demographic data, including age and race/ethnicity, and lifestyle data such as smoking were extracted from the NIS database. Comorbidities, including diabetes, obesity, renal disease, hypertension, and hyperlipidemia, were also identified by the ICD codes (Supplementary Table 1).

2.5. Statistical analysis

Since the NIS database covers a 20 % sample of the US annual inpatient admissions, weighted samples (before 2011 using

TRENDWT & after 2012 using DISCWT), stratum (NIS_STRATUM), cluster (HOSPID) were used to produce national estimates for all analyses. The SURVEY procedure in SAS was used to perform analysis for sample survey data. Descriptive statistics of female patients with **and** without HRT are presented as number (n) and weighted percentage (%) or mean and standard error (SE). Categorical data were analyzed by PROC SURVEYFREQ statement and continuous data were analyzed by PROC SURVEYREG statement.

Females using HRT and those not using it were matched by age in a case to control ratio of 1:4. Odds ratios (ORs) and 95 % confidence intervals (CIs) for factors associated with pancreatic cancer diagnosis. Covariates that reached significance in the univariate analysis were adjusted for in multivariable analysis. The Interaction p-values of the variables were calculated, and subgroup analyses were performed on the variables with Interaction p values less than 0.1. All p-values were two-sided and $p < 0.05$ was considered statistical significance. All statistical analyses were performed using the statistical software package SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population selection

This study initially extracted the data of 21,512,842 female inpatients aged ≥55 years from the NIS. Women with missing information on sample weights (n = 111,803) were excluded. Finally, 21,401,759 females were enrolled in the study. After 1:4 matching, there remained 176,545 women (with HRT: 35,309; without HRT: 141,236) for the subsequent analyses. This study sample could be extrapolated to a total of 870,404 inpatients in the entire US (Fig. 1).

3.2. Characteristics of postmenopausal women

Baseline characteristics of the study population before and after matching are summarized in Table 1. Before matching, the mean age was 73.4 ± 0.02 years. The majority were White (69.6 %), non-smoker (87.7 %), and had hypertension (62.0 %).

After matching, compared to women without HRT, those who were receiving HRT had a lower proportion of non-smokers (81.9 % vs. 86.1 %, $p < 0.001$) and had a higher proportion of Whites (82.7 % vs. 67.9 %, $p < 0.001$). For comorbidities, women who were receiving HRT had higher proportions of DM (32.4 % vs. 18.6 %, $p < 0.001$), obesity (13.5 % vs. 11.8 %, $p < 0.001$) and hyperlipidemia (35.2 % vs. 32.6 %, $p < 0.001$), and lower percentages of hypertension (54.2 % vs 60.5 %, $p < 0.001$) and CKD (11.2 % vs 16.9 %, $p < 0.001$). A significantly lower percentage of pancreatic cancer diagnosis (0.3 % vs. 0.4 %, $p = 0.003$) was observed in women receiving HRT than those who had not (Table 1).

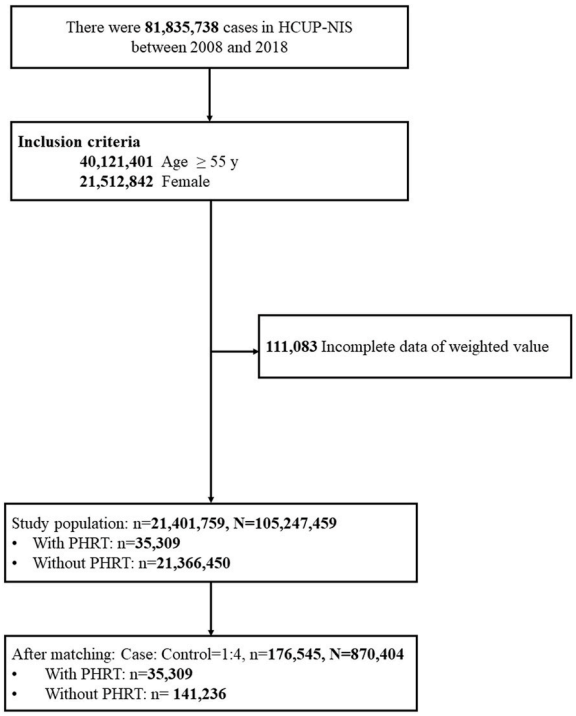

Fig. 1. Flow chart of patients' selection.

Table 1
Characteristics of the study population.

	Before matching				After matching			
	Total	With HRT	Without HRT	p-value	Total	With HRT	Without HRT	p-value
	(n = 21,401,759)	(n = 35,309)	(n = 21,366,450)		(n = 176,545)	(n = 35,309)	(n = 141,236)	
Pancreatic cancer	90674 (0.4)	105 (0.30)	90569 (0.4)	**0.004**	728 (0.4)	105 (0.3)	623 (0.4)	**0.003**
Age, years	73.4 ± 0.02	69.6 ± 0.12	73.5 ± 0.02	**<0.001**	69.8 ± 0.04	69.6 ± 0.12	69.9 ± 0.03	0.086
55–64	5420882 (25.3)	12701 (35.9)	5408181 (25.3)	**<0.001**	63505 (36.0)	12701 (35.9)	50804 (36.0)	0.999
65–74	5980882 (28.0)	11875 (33.7)	5969007 (28.0)		59375 (33.7)	11875 (33.7)	47500 (33.7)	
75–84	5781188 (27.0)	7222 (20.5)	5773966 (27.0)		36110 (20.4)	7222 (20.5)	28888 (20.4)	
85+	4218807 (19.7)	3511 (10.0)	4215296 (19.7)		17555 (9.9)	3511 (10.0)	14044 (9.9)	
Race				**<0.001**				**<0.001**
White	14876115 (69.6)	29172 (82.7)	14846943 (69.6)		125006 (70.9)	29172 (82.7)	95834 (67.9)	
Black	2431211 (11.4)	1655 (4.7)	2429556 (11.4)		19207 (10.9)	1655 (4.7)	17552 (12.5)	
Hispanic	1434546 (6.7)	1462 (4.2)	1433084 (6.7)		11333 (6.4)	1462 (4.2)	9871 (7.0)	
Others/Unknown	2659887 (12.3)	3020 (8.5)	2656867 (12.3)		20999 (11.8)	3020 (8.5)	17979 (12.6)	
Smoking				**<0.001**				**<0.001**
No	18774217 (87.7)	28972 (81.9)	18745245 (87.7)		150636 (85.3)	28972 (81.9)	121664 (86.1)	
Yes	2627542 (12.3)	6337 (18.1)	2621205 (12.3)		25909 (14.7)	6337 (18.1)	19572 (13.9)	
Comorbidity								
Diabetes	6711163 (31.4)	6558 (18.6)	6704605 (31.4)	**<0.001**	6558 (18.6)	45767 (32.4)	6558 (18.6)	**<0.001**
Obesity	2470617 (11.6)	4180 (11.8)	2466437 (11.6)	0.216	4180 (11.8)	19087 (13.5)	4180 (11.8)	**<0.001**
Hypertension	13276762 (62.0)	19179 (54.2)	13257583 (62.0)	**<0.001**	104729 (59.2)	19179 (54.2)	85550 (60.5)	**<0.001**
Renal diseases	3870910 (18.1)	3928 (11.2)	3866982 (18.1)	**<0.001**	27681 (15.7)	3928 (11.2)	23753 (16.9)	**<0.001**
Hyperlipidemia	7128266 (33.4)	12415 (35.2)	7115851 (33.4)	**<0.001**	58331 (33.1)	12415 (35.2)	45916 (32.6)	**<0.001**

Abbreviation: HRT, hormone replacement therapy.
Continuous variables are presented as mean ± SE; categorical variables are presented as unweighted counts (weighted percentage).
P-values <0.05 are shown in bold.

3.3. Associations between HRT use and pancreatic cancer

Table 2 shows the associations between pancreatic cancer and HRT use in an age-matched population. In univariate analyses, women who were receiving HRT had significantly decreased odds for pancreatic cancer (OR, 0.68, 95%CI: 0.52–0.88) than those without HRT. Age above 85 years (vs. 55–64 years), and comorbidities including diabetes, obesity, hypertension, renal diseases, and hyperlipidemia, were significantly associated with the odds of pancreatic cancer.

After adjusting for age, diabetes, obesity, hypertension, renal diseases, and hyperlipidemia, the multivariable analysis revealed that HRT was significantly associated with decreased odds for the presence of pancreatic cancer (adjusted OR [aOR], 0.69, 95 % CI: 0.53–0.90). In addition, age ≥85 (aOR, 0.64, 95 % CI: 0.46–0.90), hypertension (aOR, 0.76, 95 % CI: 0.65–0.88), and hyperlipidemia (aOR, 0.78, 95 % CI: 0.65–0.92) were significantly associated with pancreatic cancer, and all interaction p values were all less than 0.1,

Table 2
Association between HRT, demographics, comorbid conditions, and pancreatic cancer diagnosis in postmenopausal women.

Variables	Pancreatic cancer				
	OR (95 % CI)	p value	aOR (95 % CI)[a]	p value	Interaction p
HRT	**0.68 (0.52, 0.88)**	**0.003**	**0.69 (0.53, 0.90)**	**0.006**	
Age, years					
55-64	ref		ref		**<0.001**
65-74	1.11 (0.94, 1.32)	0.225	1.15 (0.97, 1.36)	0.103	
75-84	1.03 (0.84, 1.26)	0.765	1.09 (0.89, 1.34)	0.384	
85+	**0.59 (0.42, 0.82)**	**0.002**	**0.64 (0.46, 0.90)**	**0.011**	
Race					
White	ref				
Black	1.19 (0.95, 1.50)	0.132			
Hispanic	1.28 (0.97, 1.68)	0.081			
Others/Unknown	1.25 (0.98, 1.60)	0.069			
Smoking	1.03 (0.85, 1.26)	0.740			
Comorbidity					
Diabetes	**1.43 (1.23, 1.66)**	**<0.001**	**1.82 (1.55, 2.13)**	**<0.001**	0.280
Obesity	**0.47 (0.35, 0.63)**	**<0.001**	**0.44 (0.33, 0.59)**	**<0.001**	0.645
Hypertension	**0.83 (0.72, 0.96)**	**0.012**	**0.76 (0.65, 0.88)**	**<0.001**	**0.061**
Renal diseases	**0.40 (0.30, 0.53)**	**<0.001**	**0.33 (0.25, 0.44)**	**<0.001**	0.572
Hyperlipidemia	**0.76 (0.64, 0.89)**	**0.001**	**0.78 (0.65, 0.92)**	**0.004**	**0.031**

Significant values are shown in bold.
Abbreviation: HRT, hormone replacement therapy; OR, odds ratio; aOR, adjusted OR; CI, confidence interval.
[a] Adjusted for age, diabetes, obesity, hypertension, renal diseases and hyperlipidemia.

prompting us to conduct subgroup analyses according to these variables(Table 2).

3.4. Associations between HRT and pancreatic cancer diagnosis among subgroups

Table 3 shows the results of subgroup analyses on the associations between HRT and pancreatic cancer diagnosis. Compared to no HRT, HRT was significantly associated with decreased odds for pancreatic cancer among women 55–64 years of age (aOR 0.48, 95 % CI: 0.32–0.74), 65–74 years of age (aOR 0.49, 95 % CI: 0.34–0.71), but not among their older counterparts. The protective effect of HRT against pancreatic cancer was only observed in women without comorbid hypertension (aOR 0.55, 95 % CI: 0.38–0.79) and women without comorbid hyperlipidemia (aOR 0.59, 95 % CI: 0.42–0.82). In addition, HRT showed a protective effect against pancreatic cancer both among women 55–64 years and without hypertension or hyperlipidemia (aOR 0.33, 95 % CI: 0.20–0.56) and women 55–64 years who had hypertension and/or hyperlipidemia (aOR 0.61, 95 % CI: 0.43–0.85) (Table 3 & Fig. 2).

4. Discussion

The present study investigated the relationships between HRT use and the presence of pancreatic cancer diagnosis among women ≥55 years of age in the US NIS dataset. An independent association between HRT and pancreatic cancer is observed in the general women population ≥55 years of age and several subgroups. Specifically, women who were receiving HRT are less likely to have pancreatic cancer than those who did not receive HRT, particularly in the subgroups aged 55–64 and 65–74 years, and in women with no hypertension or no hyperlipidemia. These findings indicate that exogenous female hormones may have a protective effect against pancreatic cancer in postmenopausal women.

Evidence on whether there is a link between HRT use in postmenopausal women and pancreatic cancer risk is scarce and largely contradictory. Several studies reported that HRT reduced the risk of pancreatic cancer [24,29,30], whereas others reported that HRT was not a protective factor against pancreatic cancer [31,32]. Importantly, there are great disparities between these studies in many aspects including study designs, distinct study populations, baseline characteristics, and confounding factors adjusted, which may explain the conflicting findings on HRT and pancreatic cancer risk. A case-control study by Andersson et al. studied 17,035 women and reported that the use of oral contraceptives (OC) showed no significant association with the risk of pancreatic cancer. However, the use of HRT was significantly linked to a lower risk of pancreatic cancer, with an age-adjusted hazard ratio (HR) of 0.47 and a fully adjusted HR of 0.48, particularly for regimens containing estrogen only [24]. However, the interpretation of that study was greatly limited by its case-control nature which increased the possibility of selection bias, and by a substantial number of missing variables which hampered the reliability of their results. Another prior report pooled several small-sample, case-control studies from the 1980s to 2011, and found an inverse association between pancreatic cancer and hysterectomy plus hormone use [30]. Nevertheless, the authors of that study concluded that whether hormone replacement therapy alone affects the risk of pancreatic cancer is unknown.

Kabat et al. assessed the association between several reproductive factors and pancreatic cancer risk in a large number of postmenopausal women followed over 14 years [31]. Compared with nulliparous women, those with 1–2 and 3–4 births had a reduced risk of pancreatic cancer, but not women with >5 births. However, other reproductive factors and use of exogenous sex hormones were not associated with pancreatic cancer risk, and the authors concluded that reproductive and hormonal exposures were unlikely to play a significant role in the etiology of pancreatic cancer [31]. Another study by Zhang et al. examined the association between reproductive

Table 3
Subgroup analyses on the associations between HRT and pancreatic cancer diagnosis in postmenopausal women.

Subgroup	HRT	Pancreatic cancer	
		aOR (95 % CI)	p-value
Age, years[a]			
55-64	Yes vs. No	**0.48 (0.32, 0.74)**	**<0.001**
65-74	Yes vs. No	**0.49 (0.34, 0.71)**	**<0.001**
75-84	Yes vs. No	1.27 (0.84, 1.92)	0.262
85+	Yes vs. No	1.78 (0.90, 3.54)	0.100
Hypertension[b]			
No	Yes vs. No	**0.55 (0.38, 0.79)**	**0.001**
Yes	Yes vs. No	0.85 (0.62, 1.15)	0.290
Hyperlipidemia[c]			
No	Yes vs. No	**0.59 (0.42, 0.82)**	**0.002**
Yes	Yes vs. No	0.97 (0.66, 1.41)	0.870
By age and status of hypertension/hyperlipidemia[d]			
55-74y, without hypertension or hyperlipidemia	Yes vs. No	0.33 (0.20, 0.56)	**<0.001**
55-74y, with hypertension and/or hyperlipidemia	Yes vs. No	0.61 (0.43, 0.85)	**0.003**

P-values <0.05 are shown in bold.
Abbreviation: HRT, hormone replacement therapy; OR, odds ratio; aOR, adjusted OR; CI, confidence interval.
[a] Adjusted for smoking, diabetes, obesity, hypertension, renal diseases and hyperlipidemia.
[b] Adjusted for age group, smoking, diabetes, obesity, renal diseases and hyperlipidemia.
[c] Adjusted for age group, smoking, diabetes, obesity, hypertension and renal diseases.
[d] Adjusted for smoking, diabetes, obesity and renal diseases.

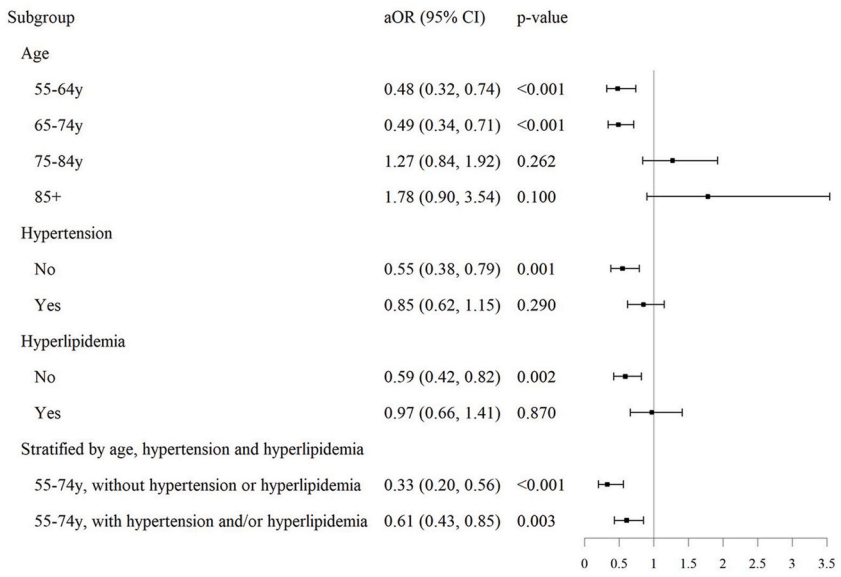

Fig. 2. Forest plot of the association between HRT and pancreatic cancer diagnosis in postmenopausal women.

factors, the use of oral contraceptives and postmenopausal hormone therapy with pancreatic cancer risk in 284 women with pancreatic cancer and 1096 controls [32]. Older age at first pregnancy and long-term use of oral contraceptives were associated with an increased risk of pancreatic cancer, whereas no significant relationships were found between pancreatic cancer risk and hormone therapy [31]. A cohort study by Lee et al. that included women in the community among public school professionals found that reproductive factors, including age at menarche, parity, breastfeeding, and age at menopause, were not associated with pancreatic cancer risk. While estrogen-plus-progestin therapy use was not associated with pancreatic cancer risk, women with longer OC use were more likely to have cancer [29].

The present study intended to address the controversy elucidated above regarding the potential impact of hormone therapy on pancreatic cancer. Our findings are more informative than earlier ones not just because they use the most rigorous matching method and query the largest sample size in the literature, but also because it include analyses in a variety of specific subgroups.

Given the findings presented in this study, one may inquire about the mechanisms underlying the associations between hormone therapy and a lower risk of pancreatic cancer. Previous animal research has investigated the potential effects of sex steroids on early pancreatic carcinogenesis in azaserine-treated rats of both sexes [33]. Significant sex differences were observed in that study, with male rats having more eosinophilic atypical acinar cell lesions and nodules than female rats, while castration resulted in the decline of eosinophilic atypical acinar cell lesions and nodules. Furthermore, when castrated male rats were treated with estradiol, a linear decrease in the number of eosinophilic atypical acinar cell foci and nodules and a dose-dependent increase in serum estradiol levels were observed. That study indicated that the administration of estrogen inhibits the development of transplantable pancreatic cancer in an animal model [33]. Another animal study explored the effect of sex steroids on the growth of azaserine-induced transplantable rat pancreatic carcinoma DSL-2 [17]. Results of that study showed castration alone or in combination with 17β-estradiol pretreatment inhibited the growth of transplantable tumors. The mechanism underlying the anti-carcinogenic effect of β-estradiol/estrogen remains under further investigation. *In vitro* studies showed that β-estradiol inhibits the proliferation of chemotherapy-refractory hepatocellular carcinoma cell lines through downregulation of IL-6/STAT3 signaling [34] and induces mitochondrial apoptosis in HeLa cells through suppression of AKT/NF-B signaling [35], which may contribute to the anti-cancer effect.

In the present study, interestingly, postmenopausal HRT use was associated with lower pancreatic cancer among non-hypertensive women but not among those with hypertension, suggesting hypertension as well as anti-hypertensive medications may be a moderating factor for the relationship between HRT and pancreatic cancer. The effect of long-term use of antihypertensive drugs, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, calcium channel blockers, and diuretics on the risk of pancreatic cancer remains unclear. A Danish cohort study by Kirkegård et al. examined the association between the use of antihypertensive drugs and pancreatic cancer risk in patients with chronic pancreatitis between 1996 and 2012 [36] but found little evidence to support an association. Further, a recent meta-analysis by Jiang et al. of whether antihypertensive medications have a negative impact on outcomes in patients with pancreatic cancer discovered that antihypertensive medications had no negative impact on overall survival in patients with pancreatic cancer, despite the fact that they may inhibit the development of pancreatic cancer [37]. Future well-design studies are warranted to address whether there are interactions between HRT, antihypertensive medications, and malignancy of the pancreas.

On the other hand, our results also showed that women with diabetes had a higher risk of developing pancreatic cancer, which aligns with findings from other studies [38,39]. However, patients with obesity, hypertension, renal disease, and hyperlipidemia showed a decreased risk of having pancreatic cancer. Notably, only hypertension and hyperlipidemia were significantly associated

with pancreatic cancer, with all interaction p-values less than 0.1, prompting us to conduct subgroup analyses. Subgroup analyses revealed that HRT shows a protective effect in women without hypertension and women without hyperlipidemia against pancreatic cancer. HRT reduced the risk among women without hyperlipidemia, suggesting a correlation with anti-hyperlipidemic medication. Statin, the most commonly used anti-hyperlipidemic agent, is reported to reduce the risk of pancreatic cancer. Several studies have shown that statin use is associated with longer survival in patients with pancreatic cancer [40]. Meanwhile, while elevated total cholesterol levels in the recent past may be associated with a reduced incidence of pancreatic cancer, a recent decline in total cholesterol levels could indicate an increased risk of developing pancreatic cancer [41]. Considering the complex relationship among hyperlipidemia, HRT use, and pancreatic cancer risk, additional research is essential to elucidate the interactions between HRT, statins, serum lipid levels, and pancreatic cancer.

The protective effect of HRT against pancreatic cancer was observed in the 55–64 and 65–74 age groups, which may be due to fewer comorbidities and a better risk-benefit balance at these ages. However, in women aged 75 and older, the increased prevalence of comorbidities such as cardiovascular disease, diabetes, and hypertension may diminish the protective effects of HRT. These comorbid conditions can complicate the health profile of older women, making the net benefit of HRT less apparent.

4.1. Limitations

The study has several limitations, including the inherent limitations of retrospective, cross-sectional study design, which limits the generalization of results to other populations, does not allow inferences of causality, and selection bias cannot be ruled out. The possibility of coding errors exists as in other studies that used ICD code systems. The NIS does not include detailed information on medications or results of laboratory testing, which limits full consideration of patients' health status and profiles of HRT. Lastly, we did not analyze specific subtypes of pancreatic cancer because the ICD codes used did not adequately capture these subtypes, leading to an insufficient number of cases for a meaningful analysis. This limitation should be addressed in future studies.

5. Conclusions

This study has demonstrated an association between HRT use and lowered pancreatic cancer in general postmenopausal women of the US, particularly in women aged 55–74 years, and those without hypertension or hyperlipidemia. Further research is needed to understand the underlying mechanisms and confirm these findings to guide clinical decisions on HRT use in postmenopausal women.

Ethics declarations

All data were obtained through a request to the Online Healthcare Cost and Utilization Project (HCUP) Central Distributor (available at: https://www.distributor.hcup-us.ahrq.gov/), which administers the database (certificate # HCUP-359L52GVU). This study conforms to the NIS data-use agreement with HCUP. Because this study analyzed secondary data from the NIS database, patients and the public were not involved directly. Review and approval by an ethics committee was not needed for this study because all data in the NIS database are de-identified, the requirement for informed consent was also waived.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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CRediT authorship contribution statement

Lei Liu: Supervision, Formal analysis, Data curation. **Xinyu Wang:** Formal analysis, Data curation. **Dekai Guo:** Formal analysis, Data curation. **Ruirui Ma:** Methodology, Investigation. **Haibing Gong:** Formal analysis, Data curation. **Congjun Wang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37588.

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