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Menstrual and Reproductive Factors, Hormone Use and Risk of Pancreatic Cancer: Analysis From the International Pancreatic Cancer Case-Control Consortium (Panc4)

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Abstract

Objectives—We aimed to evaluate the relation between menstrual and reproductive factors, exogenous hormones, and risk of pancreatic cancer (PC).

Methods—Eleven case-control studies within the International Pancreatic Cancer Case-Control Consortium (PanC4) took part in the present study, including in total 2,838 case and 4,748 control women. Pooled estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using a two-step logistic regression model and adjusting for relevant covariates.

Results—An inverse OR was observed in women who reported having had hysterectomy ($OR_{yes\ vs.no}$ 0.78, 95%CI 0.67–0.91), remaining significant in post-menopausal women and never-smoking women, adjusted for potential PC confounders. A mutually-adjusted model with the joint effect for hormone replace therapy (HRT) and hysterectomy showed significant inverse associations with PC in women who reported having had hysterectomy with HRT use (OR 0.64, 95%CI 0.48–0.84).

Conclusion—Our large pooled analysis suggests that women who have had a hysterectomy may have reduced risk of PC. However, we cannot rule out that the reduced risk could be due to factors or indications for having had a hysterectomy. Further investigation of risk according to HRT use and reason for hysterectomy may be necessary.

Keywords

Pancreatic cancer; menstrual and reproductive factors; exogenous hormones; hysterectomy; consortium

INTRODUCTION

Pancreatic cancer is the twelfth most common cancer in the world[1], but has among the poorest survival of all cancers. The aggressive nature of the disease and the lack of early markers or effective treatment options results in the lowest 5-year survival rate (3–7%) of all cancers in the US[2,3]. About 95% of pancreatic cancers are ductal adenocarcinomas (PC). Tobacco smoking is the main risk factor for PC and explains about 20% of the risk in a population where prevalence of smoking is 30%[4,5]. ABO non-O blood group, obesity, long-term type 2 diabetes, family history of PC, histories of pancreatitis and possibly heavy alcohol consumption, familial rare inherited mutations in *BRCA2*, *p16* and other genes, and common variants in at least eight genetic loci are other known PC risk factors[6–8].

PC incidence is somewhat higher in men than in women. In the US, between 2007 and 2011, the sex ratio ranged from 1.3 (for ages 40–44), to 1.1 (for ages 85 and over)[9]. In Europe, the estimated sex ratio in 2012 is highest at 1.9, for ages 40–44, and is 1.1 at ages 75 and over[10]. Some studies, using castrated rats, showed that administration of sex steroids inhibits the development and growth of preneoplastic lesions of the pancreas[11,12]. Motivated by these observations, and under the hypothesis that greater exposure to female sex hormones (through early menarche, later menopause, high number of pregnancies, and having a history of hormone use) decreases the risk of PC, several epidemiological studies have examined possible risk associations with menstrual and reproductive factors, and hormone use, but with inconsistent results. A review paper on reproductive factors and PC[13], two meta-analyses on parity[14,15], and a recent meta-analysis[16] attempted to make clear the relations

between these factors and PC risk. Comparing and summarizing previous evidence, however, is not a simple task. Inconsistencies in results may arise from different categorization and reference categories of exposure variables, different adjustment or confounding variables, and various study designs and target populations. Further, many of the previous studies were limited by small numbers of cases, and some were limited by inadequate adjustment for smoking, the primary risk factor for pancreatic cancer.

The aim of the present study was to assess whether or not menstrual or reproductive factors or hormone use are associated with risk of developing PC. Pooled individual analyses of eleven case-control studies in the PanC4 consortium allowed us to obtain precise estimates of risks and to analyze the associations in detail.

MATERIALS AND METHODS

Studies

Eleven case-control studies with information on menstrual and reproductive factors and hormone use were available within the PanC4 consortium[17–26]. At a minimum, the studies were able to provide information on age at menarche and age at menopause. The total number of women available in the combined data set were 2,838 with pancreatic cancer and 4,748 controls. The Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH), Toronto and Shanghai-I studies included proxy responders, accounting for 14.5% of the case and 4.4% of the control women (Table 1).

Exposure variables

Questions about menstrual and reproductive factors and exogenous hormone were generally similar across all the studies; however, full harmonization of the data was performed with the collaboration of the study investigators. Variables included in the analysis were: reported age at menarche, age at menopause, type of menopause (natural or surgical), history of oophorectomy, hysterectomy, age at hysterectomy, number of pregnancies, number of births (including live and stillbirths), age at first birth, number of abortions (including induced and spontaneous), history of oral contraceptive (OC) use, duration of OC use, use of menopause hormone replacement therapy (HRT), and duration of HRT. We also calculated the cumulative lifetime number of menstrual cycles, by adapting the index proposed by Chavez-MacGregor[27] as follow: for postmenopausal women, we calculated the difference between age at menopause and age at menarche; for each birth and stillbirth we subtracted cycles during 36 weeks, and 12 weeks for each abortion. Menstrual cycles absent while under OC use were assumed to last 28 days duration. For pre or perimenopausal women, we used age at recruitment instead of age at menopause. Missing age at menopause was imputed using the study-specific mean age at menopause or in case of both ovaries removed, the age at surgery.

Statistical analysis

Two-stage models were used to estimate pooled odds ratios (OR) between menstrual and reproductive factors, hormone use and PC risk. At the first stage, for each study, the association between each factor and PC risk was assessed by estimating the OR and 95%

confidence interval (CI) using study-specific logistic regression models[28]. All models in the first step were adjusted by age (<45, 45–49,50–54, 55–59, 60–64, 65–69, 70–75, ≥75 years), education (≤ 8th grade, 9th-11th grade, 12th grade or high school graduates, some college or college graduate, ≥1 year of graduate school), usual body mass index (BMI, <20, 20 to <25, 25 to <30, ≥30 kg/m^2), history of non-gestational diabetes mellitus, cigarette smoking (never-smokers, current smokers < 20 cigarettes/day, current smokers ≥20 cigarettes/day, ex-smokers < 10 years, ex-smokers ≥10 years), alcohol (no info available, 0 to <1 drink/day, 1 to < 4 drinks/day, ≥4 drinks/day), race (Non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan native) and center (for multicentric studies). History of pancreatitis was not included as an adjustment covariate in the present analysis because some of the studies observed no controls with this exposure. To account for possible differences in hormone levels during pregnancies, number of pregnancies was included when lifetime cumulative cycles was evaluated. At the second stage, pooled effect estimates across studies were calculated using random effects meta-analysis[29]. To evaluate study-based heterogeneity, we calculated the χ^2 statistic and the index *I-square*[30]. Galbraith plots were used to examine sources of heterogeneity[31], and sensitivity analyses excluding the study/studies identified with Galbraith plots were performed to evaluate study influence on pooled ORs. Studies that contributed significantly to heterogeneity in the pooled estimates for reproductive factors were excluded from the analysis of that factor. In order to account for all sources of hormone exposure at the same time, mutually adjusted models were evaluated after possible collinearity between exposure variables was assessed. Effect-measure modification by tobacco use (never, current, former), BMI (under+normal weight *vs*. obese+overweight), and histories of diabetes were evaluated using the likelihood-ratio statistic. All analyses were additionally examined restricted to postmenopausal women and to never smokers. Finally, sensitivity analyses excluding the proxy respondents and stratifying by source of control participants (population- or hospital-based) from the mutually adjusted models were also performed.

RESULTS

Table 1 gives study characteristics and distributions of the core variables according to PC status. Case subjects were older than controls, reported higher BMIs, and were more likely to be current or ex-smokers. Greater proportions of women who had had diabetes or pancreatitis were observed among cases than in controls.

To account for possible differences in the exposure variables by race/ethnicity, distributions were evaluated and only minor differences in age at menarche were observed between Asian and non-Asian ethnicities; however these differences were not statistically significant (data not shown).

All models of menstrual and reproductive factors and hormone use variables were adjusted for attained age, education, race, usual BMI, cigarette smoking, histories of diabetes and use of alcohol, and center. A statistically significant inverse association was observed in women who reported having had hysterectomy (OR 0.78, 95%CI 0.67–0.91), remaining consistent in postmenopausal and never-smoking women (Table 2). Earlier hysterectomy (≤41 years) showed non-significant inverse associations with PC risk ($OR_{\leq 37 \, vs > 52}$ 0.87; 0.53–1.42;

$OR_{>37\&\leq41\ vs\ >52}$ 0.62; 0.37–1.05) (Table 2). The observed OR for HRT users was 0.82 (95%CI 0.68–0.98) (Table 2).

Non-significant ORs below unity were observed in women who had later menarche ($OR_{>14\ vs\ <12}$ 0.85, 95%CI 0.66–1.08), bilateral oophorectomy (OR 0.83, 95%CI 0.64–1.06), used OC (OR 0.83, 95%CI 0.69–1.01), reported long-term use of HRT ($OR_{\geq36\ vs\ \text{non-users}}$ 0.81, 95%CI 0.66–1.00) or had high number of menstrual cycles ($OR_{>455\ vs\ \leq333}$ 0.74, 95%CI 0.54–1.06) (Table 2). Although the association of high number of menstrual cycles was non-significant, in the subset of never-smokers the pooled OR was 0.68 (95%CI 0.60–0.91) (Table 2). An elevated but non-significant OR was observed in women with later menopause ($OR_{\geq55\ vs\ \leq39}$ 1.32, 95%CI 0.93–1.87) (P trend=0.63). Number of pregnancies, number of births and age at first birth showed no associations with PC risk (Table 2). We also evaluated a mutually adjusted model including all sources of hormone exposure: exogenous hormones, lifetime cumulative menstrual cycles (as a summary variable for endogenous hormone exposure); and gynecological surgery: hysterectomy and oophorectomy. Since not all the studies collected all the information mentioned previously, two separate models were analyzed. Studies that contributed significantly to heterogeneity in the pooled estimates in table 2 were excluded for the mutually adjusted model. The first model included lifetime cumulative menstrual cycles, HRT and OC use; the studies that provided information were MSKCC, Central Europe and Shanghai-II. A non-significant pooled OR below unity was observed in women with more than 455 cycles compared with women with at most 333 cycles ($OR_{>455\ vs\ \leq333}$ 0.75, 95%CI 0.51–1.12); the pooled OR for HRT users was 0.87 (95%CI 0.55–1.24). A null effect was observed for OC users (Model 1; Table 3). The second mutually adjusted model included MDACC, MSKCC, Toronto, UCSF, Central Europe and SEARCH studies. For this model, the joint effect of hysterectomy and HRT use was evaluated according to the following categories: use of neither, HRT use alone, hysterectomy alone, and both hysterectomy plus HRT use (Model 2; Table 3). This joint effect variable was evaluated because the frequency of HRT use was three times as high in women who had had hysterectomies than not (data not shown). History of oophorectomy and OC use were also included in the model (Model 2; Table 3). The joint effect analysis of hysterectomy and HRT use showed that HRT use without hysterectomy conveyed a non-significant inverse association with PC ($OR_{\text{HRT}\ vs\ \text{none}}$ 0.84, 95%CI 0.64–1.10), while a significant inverse association with PC risk was observed in women with hysterectomy without HRT use ($OR_{\text{hysterectomy}\ vs\ \text{none}}$ 0.70, 95%CI 0.54–0.92) which was somewhat lower ($OR_{\text{hysterectomy+HRT}\ vs\ \text{neither}}$ 0.64, 95%CI 0.48–0.84) for women also taking HRT. No statistically significant association was observed in relation to oophorectomy. A sensitivity analysis was performed, where the joint effect was considered only when HRT use started at the same time or after the hysterectomy, however, the results did not change (data not shown). A forest plot of the study-specific and the pooled ORs for the joint effect of hysterectomy and use of HRT and PC risk is presented in Figure 1.

We found no evidence for effect-measure modification of the relation between each factor and PC risk by cigarette smoking, BMI, and history of diabetes (all likelihood ratio statistic p-values>0.05) (data not shown). Sensitivity analyses in never-smoking women and in postmenopausal women were performed, but in general, except as noted above, results did not change (Table 2 and 3). No major differences in pooled OR estimates were observed

when proxy-respondents were excluded from the mutually adjusted models or when models were stratified by the source of control participants (data not shown).

DISCUSSION

The present pooled data analysis of eleven case-control studies, including 2,838 pancreatic cancer case women and 4,748 controls, allowed us to estimate more precisely possible relations between menstrual and reproductive factors, hormone use, and PC risk. Our results suggest that undergoing hysterectomy may significantly reduce the risk of developing PC by 22%.

A non-statistically significant OR below unity was observed with high lifetime cumulative number of menstrual cycles (>455 cycles). When the analysis was restricted to never-smokers, this association became statistically significant. Lifetime cumulative menstrual cycles is an index for total exposure to endogenous hormones. Since hormonal levels differ during pregnancy, we subtracted from the calculation 36 and 12 weeks for each birth and abortion, respectively, and included the number of pregnancies as an adjustment variable; and hormone use (HRT and OC) was also included in the model. Chavez-MacGregor[27] also excluded from the calculation a 6-week absence of cycles for women who reported lactation, and they accounted for menstrual cycle irregularity. Unfortunately, this information was not available in the included PanC4 studies. Because smoking is an important risk factor for PC and may also affect sex hormone levels[32], we carried out additional analyses limited to never-smokers, though similar patterns of relative risk were observed. Obese and overweight persons have an increased risk of PC[33], and high BMI is positively associated with high estrogens levels[34], but in our analysis, different levels of BMI did not alter our OR estimations. Further analyses were also performed in postmenopausal women, and similar estimates of risk and 95%CIs were observed.

In the published literature, seven previous studies of PC collected information on oophorectomy and hysterectomy; and all case-control studies that collected this information[18–20,35] were included in the present pooled analysis. Hysterectomy prevalence in PanC4 cases is almost 28% (American studies: 33%, European studies: 21%). In the American cohort studies hysterectomy prevalence in PC cases is approximately 40%[36,37], while in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort the prevalence was almost 15%[38]. The Iowa Women's health study (IWHS) cohort showed a statistically significant increase in risk for both hysterectomy (hazard ratio (HR): 1.37, 95%CI: 1.02–1.82) and bilateral oophorectomy (HR: 1.43, 95%CI: 1.01–2.00)[39]. The EPIC cohort observed a no effect of bilateral oophorectomy and hysterectomy with ovarian conservation on PC risk[38]. The Cancer Prevention Study-II Nutrition Cohort found that hysterectomy with ovarian conservation was associated with an increased risk of PC (OR 1.48, 95%CI 1.03–2.14), although no effect of hysterectomy with bilateral oophorectomy on PC was observed (OR 0.97, 95%CI 0.69–1.37)[36]. A recent meta-analysis observed[16] an inverse association in relation to hysterectomy and PC risk in case-control studies (OR 0.77, 95%CI 0.64–0.94) and no association in cohort studies. This result in case-control studies agreed with our general findings on hysterectomy (OR 0.78, 95%CI 0.67–0.91). Discrepancies between cohort studies and case-controls studies might be explained by

selection bias in hospital-based (HB) case-control studies, however, we observed that the association between hysterectomy and PC was borderline in the population-based (PB) case-control studies (PB: OR: 0.84, 95%CI 0.69–1.01; HB: OR: 0.70, 95%CI 0.54–0.90) and results by source of controls were not considered heterogeneous (Wald statistic for heterogeneity: 1.21, p-value=0.271).

The role of HRT in relation to PC risk is not clear. While two cohort[37,40] showed non-significant inverse associations, one cohort study[41] and a case-control studies[42] showed non-significant increases in risk. Finally, two studies showed relative risk estimates for HRT close to unity[38,39]. All remaining case-control studies were included in our pooled analysis[18–20,35]. None of these studies, or our pooled analyses, were able to distinguish the type of hormone therapy used, for example, whether combinations of estrogen and progestin were used, or estrogen alone. Use patterns for type of hormone therapy have changed over the past decades, with eras of estrogen alone and estrogen plus progestin[43]. The Women's Health Initiative (WHI) randomized controlled trial findings support the hypothesis that estrogen alone or estrogen plus progestin may not have the same biological effects. The WHI observed that women who reported the combination of estrogen and progestin had an increased risk of breast cancer and a non-significant decrease in the risk of endometrial cancer[44]; while taking estrogen alone did not show an increase of breast cancer in women with hysterectomy[45]. Thus, estrogen-only HRT is usually recommended for women who have had hysterectomy[43]. To evaluate the influence of changes in the consumption patterns of HRT, we analyzed the use of HRT by study year (before 2002 *vs.* after 2002); and we observed no differences in the pooled risk estimate.

In PanC4, information on HRT type was not available; however, we did observe that the frequency of HRT use was three times as high among women who reported hysterectomy than not. Further, almost 57% of women started the HRT treatment at the age of the hysterectomy, and 30% after hysterectomy. We observed a 36% lower risk in comparison to women with intact uteri and who had not used HRT. It is possible that women who have had hysterectomy and used HRT may have lower PC risk because of other factors besides hysterectomy and HRT.

Some diseases, for which the treatment is hysterectomy, are directly related with increased female hormone levels. Almost 70% of American women[46] during their fertile life will have fibroids. In many cases, fibroids do not cause symptoms, however, they can cause abnormal bleeding, and pelvic pressure, for which hysterectomy is the recommended treatment[46,47]. Among the factors that can contribute to fibroid growth are elevated levels of estrogens and progesterone[47]. Further, women diagnosed with hyperplasia tend to undergo hysterectomy surgery[48]. Hyperplasia is associated with higher levels of estrogens and insufficient levels of progesterone, and may evolve to endometrial cancer[48]. Unfortunately, the specific reason for having a hysterectomy was not available in PanC4 data, so we could not verify if the observed protective effect that was shown with hysterectomy was due to underlying elevated estrogen levels in the mentioned diseases or to other factors related to having a hysterectomy.

Lifetime cumulative menstrual cycles is an index that attempts to summarize reproductive information, including information on menarche, menopause, pregnancies, OC and lactation. Our analytical approach allowed us to evaluate the index including these factors, with the exception of lactation. Three previous studies of pancreatic cancer have evaluated the index, but each study used a different calculation and different adjustment variables[38,39,49]. All the studies, including our analysis, found no association between lifetime cumulative menstrual cycles and PC risk, suggesting little or no effect of female hormones on PC risk.

In light of the inconsistent results between the studies on menstrual and reproductive factors, hormone use and PC risk, it is worth noting that previous studies had diverse study designs, target populations and confounder and adjustment variables; specifically, adjustments for smoking and alcohol. Furthermore, risk estimates for hysterectomy and for oophorectomy were inconsistent in our analysis with those provided by cohort studies[36,38,39], possibly caused by selection bias in case-control studies.

The main weakness of our analysis is that not all of the studies collected all of the information on menstrual and reproductive factors and hormone use. Thus, mutually adjusted models could be obtained in only 4 or 6 studies, depending on the included variables, and a model that contained all collected factors in all studies was not possible. Another weakness of our analyses is that for some variables such as age at menopause, and for OC and HRT durations, we received categorical variables from some of the studies, so cut points for these variables had to be based on the received information, or the information could not be included in the calculation of lifetime cumulative menstrual cycles. Also, time periods of studies varies from the 1980's to 2011, however, low heterogeneity between studies in each pooled OR estimation was observed. Even so, the PanC4 consortium includes a large dataset which allowed us to adjust for cigarette smoking, alcohol intake, and other potential confounding variables, and with sufficient power to estimate ORs across strata of major PC risk factors, for example, smoking, BMI, and diabetes.

In conclusion, our pooled analysis found no associations between age at menarche, menopause, lifetime cumulative menstrual cycles, oophorectomy, parity, history of OC use, and PC risk, but suggests that women who have had hysterectomy may be at lower risk of PC. Further investigations by type and formulation of HRT and reason for hysterectomy could clarify the role, if any, of hysterectomy in relation to PC risk.

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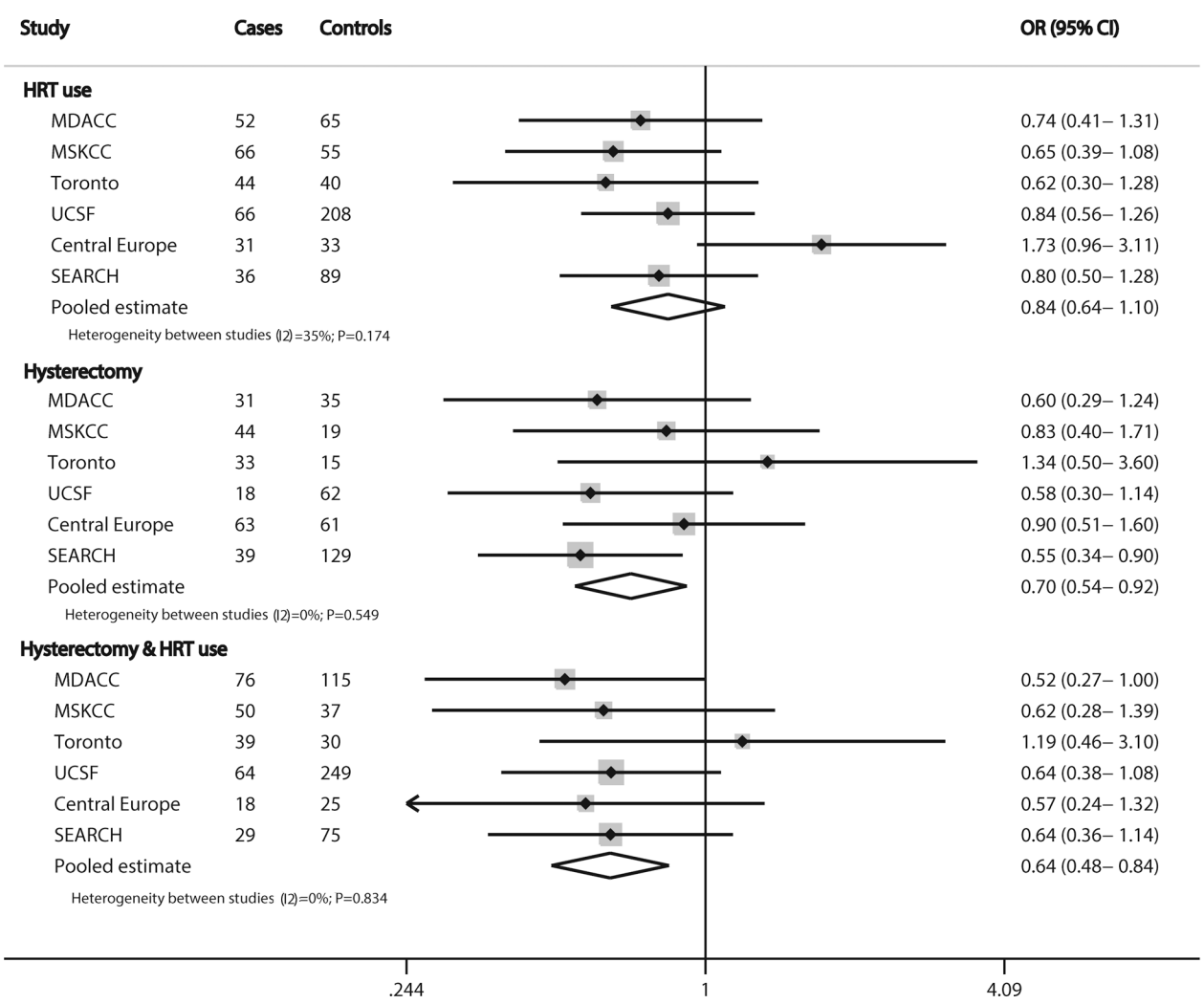

Figure 1.

Study-specific and pooled OR estimates for the associations of hysterectomy and HRT use with risk of PC in PanC4 women (Model 2; Table 3)

Footnote for figure 1: Adjusted for: age in 5-year categories, education, BMI, cigarette smoking, diabetes, alcohol, center, oophorectomy and OC use.

Box sizes are weighted by the inverse of the variance; HRT: hormone replace therapy; OC: oral contraceptive

Table 1

Studies and core variables by case and control status in PanC4 women.

		Cases n (%)	Controls n (%)	Source of controls	Type of interview
Pancreatic cancer		2838 (37.4)	4748 (62.6)		
Study	**Principal Investigator**				
North America					
MDACC (2004–2008)	Li, D	257 (9.1)	288 (6.1)	Hospital visitors	Direct
MSKCC (2003–2010)	Olson, S	424 (14.9)	242 (5.1)	Hospital visitors	Direct
Toronto (2003–2006)	Gallinger, S	217 (7.7) (6.5% proxies)	134 (2.8)	Population	Direct/ Proxy (4%)
UCSF (1995–1999)	Bracci, PM	237 (8.4)	818 (17.2)	Population	Direct
Europe					
Central Europe study; Poland, Czech Republic, Slovakia (2004–2009)	Scélo, G Holcatova, I	361 (12.7)	435 (9.2)	Population	Direct
Greece (1990–1992)	Lagiou, P	66 (2.3)	132 (2.8)	Hospital, Hospital visitors	Direct
Milan (1982–1999)	La Vecchia, C	133 (4.7)	409 (8.6)	Hospital	Direct
Italy (1991–2008)	Serraino, D	148 (5.2)	304 (6.4)	Hospital	Direct
China					
Shanghai-I (1990–1993)	Ji, B-T	187 (6.6) (29.4% proxies)	701 (14.8) (5.6% proxies)	Population	Direct / Proxy (10.6%)
Shanghai-II (2006–2011)	Risch, HA Gao, Y-T	445 (15.7)	464 (9.8)	Population	Direct
International					
SEARCH; Canada, The Netherlands, Poland, Australia (1983–1989)	Bueno-de-Mesquita, HB; Miller, AB; Baghurst, PA; Zatonski, W	363 (12.8) (58.4% proxies)	821 (17.3) (16.8% proxies)	Population	Direct / Proxy (29.6%)
Age (years)					
<45		112 (4.0)	329 (6.9)		
45–49		148 (5.2)	282 (5.9)		
50–54		228 (8.0)	488 (10.3)		

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		Cases n (%)	Controls n (%)	Source of controls	Type of interview
	55–59	371 (13.1)	675 (14.2)		
	60–64	466 (16.4)	746 (15.7)		
	65–69	544 (19.2)	832 (17.5)		
	70–75	504 (17.8)	778 (16.4)		
	≥75	465 (16.4)	618 (13.0)		
	Race				
	Non-Hispanic White	1555 (67.6)	2839 (65.6)		
	Non-Hispanic Black	46 (2.0)	54 (1.2)		
	Hispanic	18 (0.8)	53 (1.2)		
	Asian/Pacific Islander	665 (28.9)	1221 (28.2)		
	American Indian/Alaskan native	2 (0.1)	3 (0.1)		
	Other	12 (0.5)	24 (0.6)		
	Missing	1 (0.04)	133 (3.1)		
	Education				
	≤8th grade	833 (29.4)	1708 (36.0)		
	9th – 11th grade	455 (16.0)	715 (15.1)		
	12th grade/high school graduate	607 (21.4)	850 (17.9)		
	Some college/college graduate	581 (20.5)	990 (20.9)		
	≥1 year of graduate school	341 (12.0)	454 (9.6)		
	Missing	21 (0.7)	31 (0.7)		
	BMI (kg/m^2)				
	<20	319 (11.2)	623 (13.1)		
	≥20–<25	1298 (45.7)	2361 (49.7)		
	≥25–<30	801 (28.2)	1204 (25.4)		
	≥30	391 (13.8)	511 (10.8)		
	missing	29 (1.0)	49 (1.0)		
	Tobacco smoking				
	Never	1730 (61.0)	3250 (68.5)		

		Cases n (%)	Controls n (%)	Source of controls	Type of interview
Current smokers (cigarettes/day)					
<20		335 (11.8)	486 (10.2)		
≥20		142 (5.0)	113 (2.4)		
Ex-smokers (years since quitting)					
<10		141 (5.0)	223 (4.7)		
≥10		417 (14.7)	622 (13.1)		
Missing		73 (2.6)	54 (1.1)		
Alcohol drinking (drinks/day) [1]					
0 to <1		1675 (69.4)	3367 (74.7)		
1 to <4		317 (13.1)	690 (15.3)		
>=4		104 (4.3)	180 (4.0)		
missing		318 (13.2)	269 (6.0)		
History of diabetes					
No		2269 (80.0)	4391 (92.5)		
Yes		561 (19.8)	357 (7.5)		
missing		8 (0.3)			
History of pancreatitis [2]					
No		1987 (73.9)	3912 (88.0)		
Yes		123 (4.6)	49 (1.1)		
missing		580 (21.6)	483 (10.9)		

MDACC: MD Anderson Cancer Center; MSKCC: Memorial Sloan Kettering Cancer Center; UCSF: University of California, San Francisco; SEARCH: Surveillance of Environmental Aspects Related to Cancer in Humans

[1] Information not available in the MSKCC study

[2] Information not available in the Italian study

Table 2

Menstrual, reproductive factors, and hormone use in relation to PC risk in PanC4 women.

	Cases n (%)	Controls n (%)	Pooled OR (95%CI)[1]	Pooled OR (95%CI)[1] postmenopausal	Pooled OR (95%CI)[2] never smokers
MENSTRUAL FACTORS					
Age at menarche (years)					
<12[3]	343 (12.1)	571 (12.0)	0.98 (0.79–1.21)	0.96 (0.76–1.21)	0.91 (0.68–1.21)
12	467 (16.5)	783 (16.5)	reference	reference	Reference
13	634 (22.3)	949 (20.0)	1.03 (0.86–1.24)	1.05 (0.87–1.26)	1.01 (0.80–1.29)
14	475 (16.7)	871 (18.3)	0.92 (0.72–1.17)	0.92 (0.73–1.17)	0.84 (0.62–1.12)
>14	734 (25.9)	1441 (30.4)	0.85 (0.66–1.08)	0.85 (0.66–1.10)	0.85 (0.65–1.01)
Missing	185 (6.5)	133 (2.8)			
Type of menopause[4,5]					
Natural menopause	2053 (78.6)	3214 (78.7)		Reference	Reference
Surgical menopause	504 (19.3)	832 (20.4)		0.91 (0.77–1.08)	0.91 (0.74–1.11)
missing	56 (2.1)	39 (0.9)			
Age at menopause (years)[5]					
<=39	209 (7.7)	352 (8.1)		reference	reference
40–44	290 (10.7)	492 (11.3)		0.99 (0.75–1.31)	1.19 (0.81–1.77)
45–49	704 (25.9)	1120 (25.8)		1.26 (0.98–1.62)	1.41 (0.92–2.15)
50–54	1013 (37.3)	1495 (34.4)		1.27 (0.97–1.66)	1.46 (0.96–2.20)
>=55	243 (8.9)	353 (8.1)		1.32 (0.93–1.87)	1.58 (0.86–2.88)
Missing	255 (9.4)	532 (12.3)			
Lifetime cumulative menstrual cycles (cycles)[6,7]					
<=333	239 (14.1)	474 (18.6)	reference	reference	Reference
>333–383	329 (19.4)	552 (21.6)	1.01 (0.74–1.38)	0.96 (0.75–1.24)	1.01 (0.62–1.63)
>383–419	378 (22.3)	536 (21.0)	1.13 (0.87–1.46)	1.08 (0.83–1.40)	1.07 (0.70–1.63)

	Cases n (%)	Controls n (%)	Pooled OR (95%CI)[1]	Pooled OR (95%CI)[1] postmenopausal	Pooled OR (95%CI)[2] never smokers
>419–455	379 (22.3)	502 (19.7)	0.98 (0.75–1.29)	0.98 (0.74–1.28)	1.03 (0.75–1.43)
>455	336 (19.8)	468 (18.3)	0.74 (0.54–1.03)	0.75 (0.53–1.06)	0.68 (0.48–0.97)
Missing	37 (2.2)	23 (0.9)			
Oophorectomy[8]					
No	1512 (75.3)	2309 (75.9)	Reference	Reference	Reference
1 ovary removed	126 (6.3)	177 (5.8)	0.96 (0.72–1.27)	0.96 (0.71–1.29)	0.99 (0.67–1.45)
2 ovaries removed	279 (13.9)	442 (14.5)	0.83 (0.64–1.06)	0.84 (0.65–1.08)	0.77 (0.58–1.02)
Missing	90 (4.5)	114 (3.8)			
Hysterectomy[8]					
No	1361 (67.8)	1930 (63.5)	Reference	Reference	Reference
Yes	562 (28.0)	925 (30.4)	0.78 (0.67–0.91)	0.82 (0.70–0.97)	0.74 (0.60–0.91)
Missing	84 (4.2)	187 (6.2)			
Age at hysterectomy (years)[8,9]					
<=37	128 (24.3)	181 (18.7)	0.87 (0.53–1.42)	0.96 (0.57–1.62)	0.86 (0.48–1.55)
>37–41	64 (12.1)	158 (16.3)	0.62 (0.37–1.05)	0.66 (0.38–1.14)	0.51 (0.26–0.98)
>41–46	109 (20.7)	167 (17.2)	1.01 (0.53–1.91)	1.01 (0.51–2.01)	1.40 (0.79–2.47)
>46–52	90 (17.1)	163 (16.8)	0.95 (0.58–1.54)	1.01 (0.60–1.70)	0.84 (0.47–1.51)
>52	83 (15.8)	150 (15.5)	reference	reference	Reference
Missing	53 (10.1)	151 (15.6)			
Hysterectomy & Oophorectomy[8]					
None of them	1265 (63.0)	1830 (60.2)	Reference	Reference	Reference
Oophorectomy	54 (2.7)	73 (2.40)	0.91 (0.60–1.39)	0.81 (0.62–1.05)	0.83 (0.63–1.08)
Hysterectomy	206 (10.3)	366 (12.0)	0.77 (0.60–1.00)	0.85 (0.64–1.14)	0.83 (0.61–1.13)
Oophorectomy & Hysterectomy	348 (17.3)	540 (17.8)	0.79 (0.62–1.00)	0.85 (0.55–1.30)	0.73 (0.33–1.64)
Missing	134 (6.7)	233 (7.7)			

	Cases n (%)	Controls n (%)	Pooled OR (95%CI)[1]	Pooled OR (95%CI)[1] postmenopausal	Pooled OR (95%CI)[2] never smokers
REPRODUCTIVE FACTORS					
Number of pregnancies[10]					
Never pregnant	233 (9.0)	461 (10.3)	Reference	Reference	Reference
1	294 (11.4)	536 (12.0)	1.05 (0.77–1.43)	1.01 (0.73–1.40)	1.06 (0.77–1.45)
2	641 (24.8)	1,043 (23.4)	1.25 (0.86–1.83)	1.31 (0.89–1.95)	1.35 (0.87–1.68)
3	562 (21.8)	885 (19.8)	1.16 (0.92–1.45)	1.19 (0.93–1.52)	1.22 (0.89–1.68)
>=4	808 (31.3)	1,501 (33.6)	1.10 (0.79–1.52)	1.13 (0.80–1.59)	1.23 (0.83–1.82)
Missing	43 (1.7)	36 (0.8)			
Number of births (life births and stillbirth)[10]					
Never pregnant	175 (6.8)	258 (5.8)	0.93 (0.62–1.39)	0.89 (0.58–1.37)	0.83 (0.60–1.16)
Nulliparous	32 (1.2)	94 (2.1)	0.49 (0.29–0.83)	0.47 (0.28–0.81)	0.50 (0.22–1.13)
1	493 (19.1)	811 (18.2)	Reference	Reference	reference
2	788 (30.5)	1347 (30.2)	0.92 (0.77–1.10)	0.94 (0.78–1.15)	0.85 (0.70–1.03)
3	518 (20.1)	799 (17.9)	1.06 (0.86–1.29)	1.05 (0.83–1.32)	1.02 (0.82–1.26)
>=4	473 (18.3)	895 (20.1)	1.05 (0.83–1.32)	1.05 (0.81–1.37)	0.94 (0.74–1.18)
Missing	102 (4.0)	256 (5.7)			
Age at first birth (years)[10,11]					
<20	214 (11.0)	370 (10.10)	Reference	Reference	Reference
20–23	656 (33.7)	1185 (32.3)	0.98 (0.78–1.24)	1.00 (0.75–1.35)	1.02 (0.75–1.39)
24–27	509 (26.2)	1034 (28.2)	0.90 (0.70–1.15)	0.97 (0.69–1.35)	0.88 (0.63–1.22)
>27	455 (23.4)	801 (21.8)	1.01 (0.65–1.55)	1.04 (0.64–1.69)	1.07 (0.76–1.52)
Missing	110 (5.7)	277 (7.6)			
Number of abortions (induced and pontaneous)[10]					
Never pregnant	175 (6.9)	258 (5.8)	Reference	Reference	Reference
0	1361 (52.7)	2204 (49.4)	1.26 (0.82–1.96)	1.40 (0.90–2.07)	1.40 (0.91–2.41)
1	562 (21.8)	1010 (22.7)	0.98 (0.75–1.27)	1.09 (0.80–1.48)	1.03 (0.67–1.60)

	Cases n (%)	Controls n (%)	Pooled OR (95%CI)[1]	Pooled OR (95%CI)[1] postmenopausal	Pooled OR (95%CI)[2] never smokers
2	259 (10.0)	475 (10.7)	0.85 (0.55–1.33)	0.99 (0.60–1.64)	0.97 (0.53–1.80)
>=3	122 (4.7)	257 (5.8)	0.88 (0.58–1.35)	1.06 (0.68–1.65)	0.93 (0.51–1.69)
Missing	102 (3.9)	256 (5.7)			
EXOGENOUS HORMONE USE					
OC use[12]					
Non-user	1863 (67.2)	3266 (70.8)	Reference	Reference	Reference
Yes	660 (23.8)	1177 (25.5)	0.83 (0.69–1.01)	0.82 (0.65–1.02)	0.86 (0.67–1.09)
Missing	249 (9.0)	173 (3.8)			
OC duration (months)[12,13,14]					
Non-user	1568 (73.8)	2574 (71.3)	Reference	Reference	Reference
<12	78 (3.7)	176 (4.9)	0.77 (0.49–1.21)	0.79 (0.52–1.19)	0.76 (0.41–1.40)
12–<36	131 (6.2)	225 (6.2)	0.90 (0.67–1.20)	0.88 (0.65–1.19)	1.30 (0.87–1.94)
≥36	332 (15.6)	627 (17.4)	0.84 (0.67–1.06)	0.84 (0.63–1.11)	0.85 (0.64–1.13)
Missing	15 (0.7)	9 (0.25)			
HRT use[12, 15]					
No	1395 (65.2)	2251 (65.2)	Reference	Reference	Reference
Yes	632 (29.5)	1105 (32.0)	0.82 (0.68–0.98)	0.79 (0.65–0.97)	0.78 (0.58–1.05)
Missing	113 (5.3)	95 (2.8)			
HRT duration (months)[12,16]					
Non-user	1395 (68.8)	2251 (67.1)	Reference	Reference	Reference
<12	95 (4.7)	184 (5.5)	0.86 (0.55–1.33)	0.88 (0.56–1.38)	0.92 (0.61–1.39)
12–<36	128 (6.3)	182 (5.4)	1.04 (0.72–1.49)	1.04 (0.71–1.53)	0.94 (0.61–1.46)
≥36	393 (19.4)	703 (21.0)	0.81 (0.66–1.00)	0.80 (0.63–1.01)	0.75 (0.56–1.00)
Missing	16 (0.8)	36 (1.1)			

OC: Oral contraceptive use; HRT: hormone replace therapy

[1]Adjusted for: age in 5-year categories, education, BMI, tobacco smoking, diabetes (yes/no), alcohol and center

[2] Adjusted for: age in 5-year categories, education, BMI, diabetes (yes/no), alcohol and center

[3] Shanghai-I was not included in this category because there were 0 cases and 2 controls

[4] Information not available in Shanghai-I study

[5] In post-menopausal women

[6] Information not available in MDACC, SEARCH, Toronto and Greek studies. UCSF was excluded due to heterogeneity (I^2=62%)and its influence in the pooled estimates

[7] Adjusted for age 5 years categories, education, BMI, tobacco smoking, diabetes (yes/no), alcohol, center and number of pregnancies

[8] Information not available in the Milan, Greek, Shanghai-I and Shanghai-II studies

[9] Central Europe study excluded due to high heterogeneity (I^2: 53.4%) and its influence in the pooled estimations

[10] Information on parity not available in the MDACC study

[11] In parous women

[12] Information not available in the Greek study

[13] Shanghai - I study was not included due to the proportion of non-users and short-users (<6 months) was ≥95%

[14] Toronto study was not included due to the lack of controls in the highest category

[15] Shanghai-I study was not included due to the proportion of non-users was ≥95%. Italy+Milan studies were excluded due to heterogeneity (I^2=58.2%) and its influence in the pooled estimates.

[16] Milan, Italy, Shanghai-I and Shanghai-II were not included due to the proportion of non-users and short-users (<6 months) was ≥90%

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Table 3

Mutually adjusted models for cumulative number of menstrual cycles, hormone use, gynecological surgery, and PC risk in PanC4 women.

		Cases/ controls	Pooled OR (95%CI)	Pooled OR (95%CI) postmenopausal	Pooled OR (95%CI) never smokers
Model 1 [1,2]	**Lifetime cumulative menstrual cycles (cycles)**				
	<=333	161/135	reference	reference	reference
	>333–383	208/215	0.81 (0.58–1.14)	0.81 (0.58–1.15)	0.71 (0.48–1.06)
	>383–419	273/247	0.93 (0.66–1.31)	0.94 (0.67–1.32)	0.81 (0.54–1.21)
	>419–455	288/273	0.85 (0.60–1.19)	0.85 (0.60–1.20)	0.79 (0.52–1.18)
	>455	267/252	0.75 (0.51–1.12)	0.76 (0.52–1.11)	0.65 (0.42–1.01)
	Missing	33/19			
	HRT use				
	No	995/912	reference	reference	reference
	Yes	185/166	0.87 (0.55–1.39)	0.87 (0.55–1.39)	0.87 (0.53–1.42)
	Missing	60/63			
	OC use				
	Non-user	796/785	reference	reference	reference
	Yes	231/223	0.95 (0.72–1.24)	0.94 (0.72–1.23)	0.95 (0.68–1.32)
	Missing	203/133			
Model 2 [3,4]	**Hysterectomy & HRT use**				
	Neither	865/1114	reference	reference	reference
	HRT use alone	303/492	0.84 (0.64–1.10)	0.84 (0.63–1.12)	0.73 (0.46–1.15)
	Hysterectomy alone	234/323	0.70 (0.54–0.92)	0.80 (0.60–1.07)	0.57 (0.39–0.83)
	Hysterectomy and HRT use	287/534	0.64 (0.48–0.84)	0.65 (0.48–0.88)	0.55 (0.37–0.83)
	Missing	170/275			
	Oophorectomy				
	No	1611/1144	reference	reference	reference
	1 ovary removed	113/147	1.13 (0.81–1.58)	1.08 (0.77–1.53)	1.34 (0.82–2.19)
	2 ovaries Removed	269/413	1.12 (0.83–1.52)	1.09 (0.80–1.48)	1.13 (0.77–1.66)

		Cases/ controls	Pooled OR (95%CI)	Pooled OR (95%CI) postmenopausal	Pooled OR (95%CI) never smokers
	Missing	88/101			
	OC use				
	Non-user	1046/1576	reference	reference	reference
	Yes	565/990	0.78 (0.61–0.99)	0.76 (0.57–1.01)	0.83 (0.59–1.15)
	Missing	248/172			

OC: Oral contraceptive use; HRT: Hormone replace therapy

[1]Adjuster for: age in 5-year categories, education, BMI, tobacco smoking, diabetes (yes/no), alcohol, center and number of pregnancies // Never smokers model did not include tobacco smoking variable

[2]Studies included MSKCC, Central Europe, and Shanghai-II

[3]Adjusted for: age in 5-year categories, education, BMI, tobacco smoking, diabetes (yes/no), alcohol and center // Never smokers model did not include tobacco smoking variable

[4]Studies included MDACC, MSKCC, Toronto, UCSF, Central Europe, and SEARCH