THE INFLUENCE OF AGE AND GENDER ON SERUM CONCENTRATIONS OF P,P'DDT, P,P'DDE AND THE DDT / DDE RATIO IN SUBJECTS WITH EXOCRINE PANCRETIC CANCER

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Introduction

While the high lethality of exocrine pancreatic cancer (EPC) makes it a leading cause of cancer mortality in Western countries, its etiology remains largely unknown; the main risk factors identified include the advance of age, male sex and cigarette smoking.[1] Organochlorine compounds (OC) as p,p'DDT, p,p'DDE and some polychlorinated biphenyls (PCBs) have been associated with the risk of developing EPC.[2-4] DDT, an insecticide widely used in Spain during the 1970s, and DDE, its major metabolite and degradation product, are ubiquitous in the environment, have long half-lives and are found in virtually all Europeans.[5] Age is commonly associated with serum concentrations of these compounds. The DDT / DDE ratio may be used as an index of the oldness of contamination by DDT.[6] The aim of this study was to determine blood concentrations of p,p'DDT and p,p'DDE, and the DDT / DDE ratio in patients with EPC, and to analyse the influence of age and gender upon such values.

Subjects and methods

All EPC cases newly diagnosed at 5 general hospitals in eastern Spain between 1992 and 1995 were prospectively included in the PANKRAS II Study (n=185).[2] Over 88% were personally interviewed in-hospital. Serum concentrations of OC were analysed in 144 subjects by high-resolution gas chromatography with electron-capture detection. Calibration lines were calculated and the compounds were then quantified by external standard methods after replicating the analyses.[7] Samples were analysed in two periods. In 1997, serum samples from 51 subjects with EPC were analysed (phase I);[2] in 2001, analyses included samples from 93 cases (phase II). A conversion factor was obtained by lineal regression of samples with quantified values and, in order to equalise values from the two periods, it was applied to samples from phase I. In phase I limits of detection and quantitation were, respectively, 0.09 and 0.3 ng/mL for p,p'DDT, and 0.6 and 2 for p,p'DDE.[2,7] In phase II, they were 0.09, 0.14, 0.26 and 0.39. When a sample had an OC concentration below the detection threshold, it was assigned the mid-value of this limit; when it had a concentration detected but under the quantitation threshold, the mid-value between detection and quantitation limits was assigned. The standard formula by Phillips et al. was used to estimate total lipids on the basis of total cholesterol and triglycerides.[2] In statistical analyses the Kruskal-Wallis test was applied. Multivariate-adjusted odds ratios (OR) and their 95% confidence limits (CL) were computed by unconditional logistic regression. Spearman's coefficient was used in correlation analyses. The level of statistical significance was set at 0.05, and all tests are two-tailed.

Results

The median age of the 144 cases was 66.4 years. Of them, 85 were men (median age, 63.1 years) and 59, women (71.2 years). Serum concentrations of p,p'DDT and p,p'DDE, as well as the DDT / DDE ratio are shown in table 1 for all 144 EPC cases; results are given both on a whole basis (ng/mL) (parts per billion, ppb) and adjusted by serum total lipids (mg/g) (parts per million, ppm); the latter, in order to minimise potential confounding by lipid mobilization.[3] All cases had detectable concentrations of p,p'DDE, and 91% had detectable concentrations of p,p'DDT.

Among men, concentrations of p,p'DDT and p,p'DDE (median, mg/g) were 0.34 and 2.56, and the DDT / DDE ratio was 0.13. The corresponding values women were 0.49, 2.71 and 0.15. These differences were not statistically significant, and further decreased after adjusting for age.

Table 1. Serum concentrations of p,p'DDT and p,p'DDE, and DDT / DDE ratio among 144 subjects with exocrine pancreatic cancer (PANKRAS II Study, eastern Spain)

	Detection (%)	**Concentrations**	
		Crude (ng/mL)	**Lipid-ajusted** (µg/g)
p,p'DDT			
Detected	91.0		
Detected and quantified	80.6		
Detected and non-quantified	10.4		
Non-detected	9.0		
Median		2.92	0.42
Mean		4.58	0.72
SD		6.01	1.12
p,p'DDE			
Detected	100		
Detected and quantified	98.2		
Detected and non-quantified	2.8		
Non-detected	0.0		
Median		19.48	2.68
Mean		27.14	4.16
SD		25.06	4.39
DDT / DDE ratio			
Median		0.14	0.14
Mean		0.23	0.23
SD		0.29	0.29

There were 65 cases aged less than 66 years and 79 subjects older than 65 years. Among older subjects, concentrations of p,p'DDT and p,p'DDE (median, mg/g) were 0.52 and 2.72, and the DDT / DDE ratio was 0.17. The corresponding values for subjects less than 65 years were 0.23, 2.61 and 0.10. Thus, as compared to younger subjects, older subjects had significantly higher concentrations of p,p'DDT ($p = 0.01$) and, as a consequence, a higher DDT / DDE ratio ($p<0.01$). The older group was 3 times more likely to be in the upper tertile of p,p'DDT concentrations than the younger group (OR = 3.00, 95 % CL: 1.30 - 6.90). People over 65 years were over four times more likely to be in the upper tertile of the DDT / DDE ratio than younger cases (OR = 4.30, 95 % CL: 1.82 - 10.16).

The analyses stratifying by age (above/below 65 years) (table 2) confirmed that there were no statistically significant differences in the concentrations of p,p'DDT, p,p'DDE and the DDT / DDE ratio between women and men in either age group. Nonetheless, males over 65 years were 47 % less likely to be in the upper tertile of the DDE concentrations than females over 65 years (OR = 0.53, $p>0.05$) (table 2).

In the group of older men, concentrations of p,p'DDT were 118% higher than in younger men; among women, the corresponding figure was 68.7 % (older *versus* younger women). For p,p'DDE the difference was not as high: it was 23.7 % in the older group of men with respect to the younger group, and 7.3% in the older group of women with respect to the younger group.

Spearman's correlation coefficient between p,p'DDT and age was 0.239 ($p<0.01$); this association was somewhat stronger than that of age with p,p'DDE and with the DDT / DDE ratio (table 3). These correlations were similar for women and men. Although linear regression coefficients (â) were weak,

they were positive and statistically significant in all cases. The R^2 coefficients were also low, the highest being for p,p'DDE.

Table 2. Concentrations of p,p'DDT and p,p'DDE, and DDT / DDE ratio in 144 patients with exocrine pancreatic cancer (mg/g).

		=65 years						>65 years			
	(µg/g)	Men (N=47)	Women (N=18)	p	OR*	(95% CL)	(N=38)	Men (N=41)	Women p	OR*	(95% CL)
p,p'DDT											
Median		0.22	0.32	0.32				0.48	0.54	0.26	
Mean		0.49	0.49					0.76	1.02		
SD		0.66	0.48					1.13	1.58		
Tertiles (%)	<0.206	44.70	33.30		1*			23.70	19.50	1*	
	0.206-0.574	25.50	44.40		0.43	(0.12-1.53)	36.80	34.10		0.89	(0.27-2.97)
	>0.574	29.80	22.20		1.00	(0.24-4.20)	39.50	46.30		0.70	(0.22-2.26)
p,p'DDE											
Median		2.06	2.60	0.84				2.55	2.79	0.41	
Mean		3.87	3.17					4.46	4.62		
SD		3.59	2.38					5.89	4.32		
Tertiles (%)	<1.441	31.90	22.20		1*			31.60	24.40	1*	
	1.441-3.970	34.00	50.00		0.47	(0.12-1.87)	36.80	29.30		0.97	(0.31-3.09)
	>3.970	34.00	27.80		0.85	(0.19-3.79)	31.60	46.30		0.53	(0.17-1.59)
Ratio											
Median		0.10	0.12	0.12				0.17	0.18	0.67	
Mean		0.17	0.17					0.28	0.28		
SD		0.26	0.14					0.36	0.28		
Tertiles (%)	<0.097	53.20	33.30		1*			23.70	19.50	1*	
	0.097-0.210	27.70	38.90		0.45	(0.12-1.60)	34.20	39.00		0.72	(0.22-2.40)
	>0.210	19.10	27.80		0.43	(0.11-1.77)	42.10	41.50		0.84	(0.26-2.70)

p: p-value (Kruskal-Wallis test). *OR: Odds ratio; an OR equal to 1 denotes the reference category.

Discussion

The finding that there were no significant differences in concentrations of p,p'DDT, p,p'DDE and the DDT / DDE ratio between women and men (table 2) is in accordance with most studies, although other results suggest the existence of sex-linked factors in exposure or accumulation of OC.[8]

Older cases had higher concentrations of both OC, especially DDT and, as a consequence a higher DDT / DDE ratio. Increasing concentrations of this two OC with age have been reported by other studies in both adipose and blood samples.[4,8-12] The association seems to be explained by the period of exposure (calendar-time) and the long half-life of this compounds in humans, as well as by the relative ineffectiveness of the hepatic biotransformation and the renal elimination of highly lipophilic OC.[4,10,11] This is particularly the case of the DDT, an extensively used insecticide in Spain until it was banned in 1977, to which older subjects were hence exposed for a longer period than younger individuals.[5] The ratio DDT / DDE decreases with time after exposure due to the elimination kinetics of DDT.[10] The exposure of the general population to DDE is continuous, predominantly from the fat components of foods of animal origin.[5] The lower DDT / DDE ratio in younger subjects may reflect the relative success of the prohibition of DDT.

Although in humans concentrations of DDT show a decresing trend in many countries, in Spain values for DDE seem fairly constant or decreasing slightly.[5] As for other OC, in Spain temporal trends for concentrations of DDT and DDE in humans have not been systematically analysed yet. Large data gaps, the limited number of subjects studied and inappropriate reporting of methods by some studies

Table 3. Correlations between age and p,p'DDT, p,p'DDE and the DDT / DDE ratio

	Rho	p	ß	SE	p	R^2
All cases						
p,p'DDT	0.239	0.004	0.0070	0.007	<0.001	0.391
p,p'DDE	0.129	0.123	0.4040	0.310	<0.001	0.536
Ratio	0.196	0.019	0.0003	0.000	<0.001	0.401
Men						
p,p'DDT	0.189	0.061	0.0586	0.007	<0.001	0.383
p,p'DDE	0.107	0.294	0.3750	0.039	<0.001	0.478
Ratio	0.172	0.088	0.0035	0.000	<0.001	0.347
Women						
p,p'DDT	0.184	0.122	0.0685	0.011	<0.001	0.361
p,p'DDE	0.147	0.219	0.3540	0.370	<0.001	0.551
Ratio	0.112	0.349	0.0033	0.000	<0.001	0.497

Rho: Spearman's rank correlation coefficient

make the scientific assessment of temporal trends problematic.[5]

Only this[2] and another study[4] have analysed blood concentrations of p,p'DDT and p,p'DDE in patients with EPC. Levels of the two compounds were in our study higher than those observed by Hoppin et al.[4] Specifically, the concentrations in ng/mL of p,p'DDT were six times higher in our patients, and the concentrations of p,p'DDE were nearly three times higher. Research is ongoing to further elucidate the etiologic significance of OC in EPC.

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