HEXACHLOROBENZENE (HCB) AND TOTAL POLYCHLORINATED BIPHENYLS (3PCBS) IN HUMAN BREAST LIPIDS AND BREAST CANCER RISK IN POLISH WOMEN

Pawel Strucinski[1], Jan K. Ludwicki[1], Katarzyna Goralczyk[1], Bogdan Wojtyniak[2], Wlodzimierz Olszewski[3], Brian Buckley[4], Katarzyna Czaja[1], Jozef Jethon[5], Joanna Baranska[3] and Agnieszka Hernik[1]

[1]Department of Environmental Toxicology, National Institute of Hygiene, 24 Chocimska Street, 00-791 Warsaw, Poland
[2]Department of Medical Statistics, National Institute of Hygiene, Warsaw, Poland
[3]Department of Pathology, Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland
[4]Environmental and Occupational Health Sciences Institute, Piscataway, NJ 08854, USA
[5]Department of Plastic Surgery, Medical Center of Postgraduate Education, Warsaw, Poland

Introduction

During the last few years there has been widespread scientific and public debate concerning a new threat to human health posed by the chemicals that mimic or interfere with the normal functions of the hormonal system, called "Endocrine disruptors". The attention has focused primarily on the potential association between environmental exposure on weakly estrogenic persistent organochlorine compounds, e.g. polychlorinated biphenyls (PCBs), DDTs, HCHs, HCB or dioxins and rising trends in female breast cancer incidence in several populations[1-3]. It has been hypothesized that these compounds may play a role in the etiology of mammary gland neoplasms *via* both direct and indirect carcinogenesis mechanisms, including an estrogen-mimetic route, induction of different forms of CYP enzymes, alternating estrogen pathways, modulation of signal transduction, and activation of AhR-mediated response[1, 3-5]. Over the last few years, numerous epidemiological studies concerning the possible impact of environmental exposure to persistent organochlorine compounds on increased risk of breast cancer have been performed [6-12]. As their results are conflicting there is a lack of sufficient evidence implicating organochlorines in this disease, so this intriguing and controversial hypothesis requires further research. The results presented here, to authors' knowledge, are from the first such epidemiological case-control study performed in Central and Eastern Europe.

Methods and materials

The purpose of this study, approved by the ethical committee, was to investigate whether female breast cancer risk is associated with body burdens of non-agricultural persistent organochlorine pollutants - HCB and ΣPCBs. A total of 209 samples, of surgically removed adipose tissue from women's breasts were assayed. The specimens were obtained from 1997 to 2001 in two Warsaw's hospitals. 165 breast cancer patients suffered mainly from invasive infiltrating ductal and lobular tumours. The control group was comprised of 54 women suffering from benign breast disease or undergoing plastic surgery, none of whom had a history of previous cancer. The diagnoses, both cancer and control, were histopatologically confirmed. The available data concerning the patients (e.g. age, place of residence, menopause, etc.) was obtained from the individual medical records.

The identification and quantification of HCB and ΣPCBs (calculated as Aroclor 1254) in adipose tissue samples was performed in Department of Environmental Toxicology of the National Institute of

Hygiene in Warsaw. The analytical procedure included analyte extraction with n-hexane, clean-up with concentrated sulphuric acid (for HCB) following dehydrochlorination and oxidation (for PCBs). Finally, the analysis was carried out by GC-ECD and GC-MS.

Statistical comparisons of HCB and PCBs levels in cases and controls were made by two-sided Student's test. To examine the association between patient's age and the levels of compounds we carried out a regression analysis for both groups. Relative risks were calculated as odds ratios (ORs), estimated by multiple logistic regression with HCB and ΣPCBs exposure divided into three subgroups with tertiles as cut-off points.

Results and discussion

All women had measurable concentrations of analyzed compounds. Mean concentrations of HCB and ΣPCBs in women who were diagnosed with breast cancer were elevated (statistically significant for HCB, $p \leq 0,05$) comparing to controls (Table I). This however, may be explained by the differences in mean age of donors in both groups – cases (mean age 56,5±12,4) were significantly older ($p \leq 0,05$) than the controls (mean age 48,8±9,9).

Similarly to mean concentrations, the unadjusted ORs for both compounds (excluding 3rd tertile for ΣPCBs) showed a positive relationship between their body burden and breast cancer risk (Table II). Preliminary analyses of available data concerning potential confounders, allowed us to use age and place of residence as significant confounding factors in final logistic regression model. The

Table I. Breast tissue levels of HCB and ΣPCBs levels in cases and controls (mg/kg of lipids)

		Case group	Control group	All donors
HCB	Mean ± SD	0,0612 ± 0,0289	0,0468 ± 0,0234	0,0576 ± 0,0283
	Median	0,0566	0,0396	0,0532
	Range	0,0201 – 0,1909	0,0163 – 0,1213	0,0163 – 0,1909
ΣPCBs	Mean ± SD	0,5081 ± 0,2957	0,4303 ± 0,2979	0,4886 ± 0,2975
	Median	0,4573	0,3371	0,4500
	Range	0,0797 – 1,8451	0,0611 – 1,3396	0,0611 – 1,8451

Table II. Risk of breast cancer in relation to HCB and ΣPCBs adipose tissue levels in tertiles – unadjusted odds ratio ([a] - reference group)

	Organochlorines concentration (mg/kg of lipids)	Cases/controls	Unadjusted OR	95% CI
		HCB		
I	< 0,0401	43/29	1[a]	-
II	0,0401 – 0,0655	61/13	3,165	1,477 - 6,779
III	> 0,0655	61/12	3,428	1,575 - 7,462
		ΣPCBs		
I	< 0,3196	48/24	1[a]	-
II	0,3196 – 0,5617	58/13	2,231	1,027 - 4,846
III	> 0,5617	55/17	1,618	0,778 - 7,462

relationship between age and concentration of analyzed compounds displayed a similar pattern in both groups (Figure 1). The adjusted ORs showed increased risk of breast cancer associated with elevated body burden of HCB (all donors, 2nd tertile) as well as in group of postmenopausal women (3rd tertile) (Table III). The ORs for the other tertiles were generally elevated, especially for postmenopausal women, but not statistically significant.

In few published studies where the adipose tissue was used, the potential impact of HCB on breast cancer risk has not been observed [6,7,9,10]. However, Liljegren et al.[8] have found for HCB the higher risk in postmenopausal women with ER+ cancer. Sample-size limitation did not allow us to check this observation. Similarly to HCB, most authors have found lack of convincing association between breast

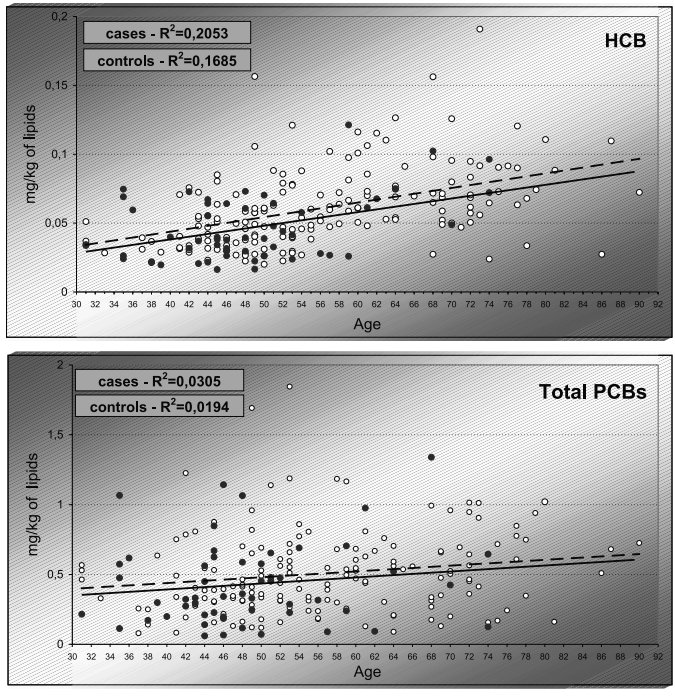

Figure 1. Relationship between HCB and ΣPCBs levels and age of donors. White circles represent breast cancer patients, and black circles represent control subjects. Solid and broken lines represent trends for control subjects and breast cancer patients respectively.

cancer and total PCBs[8,12]. However Falck et al.[6] reported that cases had higher levels of these compounds than controls. On the other hand, increased breast cancer risk associated with the breast adipose tissue concentration has been reported for some specific PCB congeners or groups of congeners[7,9,11]. The inconclusive results for PCBs can be explained by different toxicities of the individual congeners, depending on their conformation.

Due to sample-size limitations, it has not been possible to finally conclude whether analyzed compounds are or are not involved in the pathobiology of breast cancer. These results, however, support the hypothesis that long-term exposure to organochlorine compounds may be associated with a small increase in the risk of breast cancer, especially among postmenopausal women.

Table III. Risk of breast cancer in relation to HCB and ΣPCBs adipose tissue levels in tertiles –odds ratio adjusted for age and place of residence ([a] - reference group)

	All donors	Premenopausal women		Postmenopausal women	
Tertile	Adjusted OR (95 % CI)	cases/ controls	Adjusted OR (95 % CI)	Cases/ Controls	Adjusted OR (95 % CI)
HCB					
I	1[a]	31/20	1[a]	12/7	1[a]
II	2,295 (1,023-5,150)	18/5	2,055 (0,634-6,664)	42/7	3,468 (0,983-12,231)
III	1,935 (0,782-4,786)	8/6	0,814 (0,238-2,780)	53/6	4,557 (1,149-18,076)
Σ PCBs					
I	1[a]	20/14	1[a]	28/9	1[a]
II	1,938 (0,855-4,134)	22/7	1,997 (0,640-6,071)	36/5	2,070 (0,596-7,190)
III	1,113 (0,507-2,445)	12/10	0,683 (0,219-2,127)	42/6	1,799 (0,555-5,834)

Acknowledgments

The perfect technical assistance of Mrs. Grazyna Korzybska and Mrs. Danuta Zurek is gratefully acknowledged.

References

1. Davis D.L., Bradlow H.L., Wolff M., Woodruff T., Hoel D.G. and Anton-Culver H. (1993) Environ. Health Perspect. 101, 372
2. Hunter D.J. and Kelsey K.T. (1993) J. Natl. Cancer Inst. 85, 598
3. Musgrave M.A., Aronson K.J., Narod S., Hanna W., Miller A.B. and McCready D.R. (1999) Surg. Oncol. 7, 1
4. Davidson N.E. and Yager J.D. (1997) J. Natl. Cancer Inst. 89, 1743
5. Sonnenchein C. and Soto A.M. (1998) J. Steroid Biochem. Mol. Biol. 65, 143
6. Falck Jr. F., Ricci Jr. A., Wolff M.S., Godbold J. and Deckers P. (1992) Arch. Environ Health 47, 143
7. Güttes S., Failing K., Neumann K., Kleinstein J., Georgii S. and Brunn H. (1998) Arch. Environ. Contam. Toxicol. 35, 140
8. Liljegren G., Hardell L., Lindström G., Dahl P. and Magnuson A. (1998) Eur. J. Cancer Prev. 7, 135
9. Moysich K.B., Ambrosone C.B., Vena J.E., Shields P.G., Mendola P., Kostyniak P., Greizerstein H., Graham S., Marshall J.R., Schisterman E.F. and Freudenheim J.L. (1998) Cancer Epidemiol. Biom. Prev. 7, 181
10. Zheng T., Holford T.R., Mayne S.T., Tessari J., Owens P.H., Zahm S.H., Zhang B., Dubrow R., Ward B., Carter D. and Boyle P. (1999) Cancer Epidemiol. Biom. Prev. 8, 407
11. Aronson K.J., Miller A.B., Woolcott C.G., Sterns E.E., McCready D.R., Lickley L.A., Fish E.B., Hiraki G.Y., Holloway C., Ross T., Hanna W.M., SenGupta S.K. and Weber J.-P. (2000) Cancer Epidemiol. Biom. Prev. 9, 55
12. Zheng T., Holford T.R., Tessari J., Mayne S.T., Owens P.H., Ward B., Carter D., Boyle P., Dubrow R., Archibeque-Engle S. And Zahm S.H. (2000) Am. J. Epidemiol. 152, 50