



Mammographic findings and occupational exposure to pesticides currently in use on Crete

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Abstract

This is a preliminary report of an outreach mammographic-screening programme on Crete. The screening is part of a study to test if occupational exposure to pesticides in greenhouses (mainly organophosphates and organocarbamates), may increase the risk of malignant or premalignant findings in mammographic examination. A total of 1062 women (aged 40–75 years) were recruited between 1988 and 1993 and followed-up until 1998: 522 worked for at least 10 years in greenhouses for more than 4 h daily (exposed), and 540 never worked in agriculture (non-exposed). Statistics include detection rates and relative risks of mammographic findings. ‘Exposed’ women had a significantly ($P < 0.05$) higher risk than ‘non-exposed’ for fibroadenoma, ductal hyperplasia, sclerotic adenosis, fibrohyperplastic disease, cystic disease and inflammatory mastitis. There were no significant differences in the detection rates of fibrocystic changes, lipoma and malignant changes or malignant tumours. Compared with older women (aged 50–75 years), younger women (aged 40–49 years), particularly in the ‘exposed’ group, had a higher detection rate of malignant tumours. These preliminary results indicate that ‘exposed’ women may have higher risks of incidence for a number of lesions, which are risk markers for subsequent invasive breast cancers. They confirm also that early screening for breast cancer is effective and provides an opportunity for a reduction in breast cancer mortality. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Epidemiological studies imply that hormones, genetic factors and environmental agents are important risk factors in breast carcinogenesis [1]. Among the latter, a wide variety of occupational chemicals used in greenhouses, particularly organochlorines, have the ability to mimic the actions of oestrogens in the body. Even though their use has stopped, their residues in human adipose tissues may be an important aetiological factor in breast cancer. Several recent case-control studies, cohort-nested or otherwise, examined the link between organochlorines and breast cancer, but the results were not consistent [2–6]. Recent studies on oestrogen receptor-positive MCF-7 human breast cancer cells, have

revealed that oestradiol and dichlorodiphenyltrichloroethane (DDT) induced the growth of pre-neoplastic breast epithelial and breast cancer cells [7,8].

Organophosphates and organocarbamates are the main pesticides used today. Triazines and pyrethroids are also common. No known results relate organophosphate or organocarbamate exposure to risk of breast cancer. However, a recent ecological study indicated a potential link between exposure to triazine herbicides and breast cancer [9], and two studies suggested certain pyrethroid insecticides (widely used for indoor pest control), have significant oestrogenic activity. Exposure to high concentrations may pose a carcinogenic risk [10,11].

Against this background, improved mammographic screening techniques offering early diagnosis, may benefit women exposed to the intensive use of these chemicals in greenhouses. More specifically, the identification of certain structural characteristics of the breast (Wolfe’s predictive signs), mammary gland mass and

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high breast density parenchymal pattern, in mammography are all known to be positively associated with high risk patterns for breast cancer [12,13].

The main purpose of the study was to evaluate with a population-based mammographic mass screening programme the debatable evidence that occupational exposure to pesticides currently in use, may increase the risk of breast cancer. This preliminary report presents descriptive results of the mammographic findings; to quantify the risk, if any, of risk markers for subsequent invasive breast cancer developing in 'exposed' women.

2. Patients and methods

Crete is the largest island of Greece (8331.23 km²) with a population of 536 980 (1991 Census). The population is predominantly rural or semi-rural, concerned mainly with farming, but also some business and tourism. In certain areas, most farmers work exclusively in greenhouse agriculture. This involves spraying various pesticides for 2–3 h per week for 9 months per year. The whole family can be involved in tasks inside the greenhouse. Intensive greenhouse agriculture began on Crete in the mid-1960s. Organophosphates and organocarbamates are used in large quantities; triazines, pyrethroids and other chemicals such as paraquat, diquat and methylbromide are used in smaller quantities.

The data in this report are the first cohort of an outreach breast cancer-screening programme of women who were at higher than average risk. It started in 1988 and is ongoing. It is conducted by the Venizelion Hospital Mammography Unit of Heraklion (opened in 1984); it was the only such public service on Crete until 1995. Media campaigns and presentations to local meetings sought to increase awareness of screening and accessibility criteria.

The entire cohort comprised 1062 women who had a mammogram for the first time between 1988 and 1993 (accrual period). Two distinct groups were selected: 522 women with at least 10 years work in greenhouses for more than 4 h daily (exposed), and 540 women who were residents of large towns with non-agricultural occupations (non-exposed).

The inclusion in either group was also based on an initial assessment of risk made after a personal interview by two of the authors. Information was gathered on age, family history of breast cancer, history of benign breast disease, age at menarche (≤ 12 years), menopausal status and age at menopause (≥ 55 years), oral contraceptive use, menopausal oestrogen use, parity (null), age at first birth (≥ 25 years), obesity and positive physical examination. All women interviewed, who fitted the exposed/non-exposed description, were aged 40 years or older [1] and satisfied one or more of the above mentioned factors, were included in the cohort. Sec-

ondary inclusion criteria were: normal full blood count, liver function tests and biochemical profile, and Karnofsky performance status of 100.

All women were re-evaluated with mammography every 1 or 2 years, depending on positive or normal findings, until 1998. The follow-up period was at least 5 years after first examination (average 7.8 years, range 5–10 years). Six exposed and three non-exposed women were lost to follow-up and excluded from the analysis. The complete cohort was 1053 women, grouped according to exposure to occupationally used pesticides in greenhouses: 516 exposed and 537 non-exposed. The screening programme was approved by the Ethics and Scientific Committee of the Venizelion Hospital first in 1988 and in 1993 (first review). All women gave their informed consent to participate in the study.

All women were submitted to cranio-caudal and medio-lateral view for each breast with a dedicated unit low-dose mammography and high-sensitivity screen-film techniques. Medical clinical examination was performed in every case. Each woman was examined both sitting-up and lying down to confirm masses felt on the sitting-up position, and to better detect lesions lurking deeper in the breast or against the chest wall. Careful inspection of both breasts was made including size, form and symmetry, changes in pigmentation, scaling or discharge from the nipple, and detection of veins or oedema on the skin. The location, size, consistency, tenderness and mobility of the palpable tumour in each mammary gland were recorded in every case. In addition to breast palpation, careful evaluation of the axilla and supraclavicular nodal areas was a standard clinical procedure. The number, consistency, tenderness, mobility or fixation and the size of lymph nodes were also recorded. Following mammography 137 women (69 exposed and 68 non-exposed) had sonography with excisional biopsy after needle localisation. Their selection was made according to established criteria such as dense breasts, dense and poorly demonstrated areas on the mammograms, and differentiation of masses into cystic or solid. All samples were histologically examined.

The detection rates of all mammographic and histological findings (the worst read-out of all evaluations) of the two groups were compared. In particular, the presence of adeno-connective (high-density parenchymal pattern), fibro-fatty and fat tissue, as well as the detection of fibroadenoma, fibrocystic/cystic disease, hyperplasia of intraductal components or of tubular structures and malignant changes were studied.

2.1. Statistical analysis

Detection rates of the above mammographic signs for each group are expressed as proportions of positives over the entire 10-year study period (1988–1993 accrual, 1993–1998 follow-up). The difference of these rates

between the two groups was assessed by the chi-square test for contingency tables. The relative risk, estimated by the odds-ratio, and its 95% confidence interval (CI) were used to quantify further the above association [14,15].

3. Results

The sample was stratified according to age (mean 53.8 years, range 40–75 years). Table 1 shows the age and group cross-classification. The age distributions of the two groups were very similar; the association between group and age was not significant ($\chi^2 = 3.633$, degrees of freedom (d.f.) = 2, $P = 0.162$).

Table 2 shows the distribution of women according to breast tissue component and age for each group. There was a highly significant association between breast tissue component and age in both groups: exposed ($\chi^2 = 317.764$, d.f. = 4, $P < 0.0001$), non-exposed ($\chi^2 = 339.684$, d.f. = 4, $P < 0.0001$). This relationship was similar for both groups, due to the increasing proportion of fatty components in older age, and the large proportion of fibroadeno components in the 40–49 year age group. The association between the breast tissue component and group (irrespective of age) was not significant ($\chi^2 = 1.061$, d.f. = 2, $P = 0.588$), suggesting that exposure to occupationally used pesticides does not affect the general pattern of breast tissue component.

Table 3 summarises each mammography finding, by age and group.

- *Fibrocystic changes*: the difference in the detection rates of the exposed group (9.9%, 51 women) and the non-exposed (7.4%, 40 women) was not significant ($\chi^2 = 1.89$, d.f. = 1, $P = 0.169$). All 91 cases of fibrocystic changes were in women aged 40–59 years, consistent with other studies [16].
- *Ductal hyperplasia (without atypia)*: the difference in the detection rates of the exposed group (7.0%, 36 women), and the non-exposed group (3.7%, 20 women) was significant ($\chi^2 = 5.42$, d.f. = 1, $P = 0.020$). The relative risk was 1.87 with a 95%

CI of 1.1–3.13, indicating that the exposed women had a significantly higher risk of ductal hyperplasia, almost double that of those non-exposed. Again, all 56 (5.3%) identified cases of ductal hyperplasia were in women aged 40–59 years.

- *Fibrocystic and ductal hyperplasia (both present)*: the difference in the detection rates of the exposed (13.8%) and non-exposed (7.4%) was highly significant ($\chi^2 = 10.88$, d.f. = 1, $P = 0.001$). The relative risk was 1.85 with a 95% CI of 1.3–2.6. For fibrohyperplastic disease, exposed women had almost double the risk of the non-exposed group.
- *Fibroadenoma*: the difference in the detection rates of the exposed group (2.7%) and the non-exposed (0.6%) was highly significant ($\chi^2 = 7.62$, d.f. = 1, $P = 0.005$). The relative risk was 4.86 with a 95% CI of 1.4–16.7; women in the exposed group had a significantly higher risk (approximately 5 times higher) of fibroadenoma than the non-exposed group. Fibroadenoma was only detected in those aged 40–49 years.
- *Inflammatory mastitis (bacterial, traumatic)*: the difference in the detection rates of the exposed group (6.6%) and the non-exposed (3.0%) was significant ($\chi^2 = 7.46$, d.f. = 1, $P = 0.006$). The relative risk was 2.21 with a 95% CI of 1.2–4.0. Exposed women had more than double the risk of inflammatory mastitis compared with those in the non-exposed group.
- *Gross cystic disease*: the presence of solitary or multiple cysts was confirmed by combined ultrasound and mammography. As expected, most cases were found in the older age groups. The difference in the detection rate of the exposed group (16.7%) and the non-exposed (11.5%) was significant ($\chi^2 = 5.52$, d.f. = 1, $P = 0.019$). The relative risk was 1.44 with a 95% CI of 1.1–2.0, indicating that exposed women had a significantly higher risk (1.5 times higher) of gross cystic disease than non-exposed women.

Precise radiographical delineation of the *non-hyperplastic fibrosis plus adenosis (lobular hyperplasia)*, a condition labelled by pathologists as *sclerosing adenosis*, is difficult to confirm with a high degree of certainty in mammography. In this study, the difference in the detection rates of the exposed group (7.4%) and the non-exposed (3.9%) was significant ($\chi^2 = 5.82$, d.f. = 1, $P = 0.016$). The relative risk was 1.88 with a 95% CI of 1.1–3.1. Exposed women had a significantly higher risk of non-hyperplastic fibrosis plus sclerosing adenosis — almost double that of non-exposed women.

- *Lipoma*: the difference in detection rates of the exposed group (4.5%) and non-exposed (3.4%) was not significant ($\chi^2 = 0.82$, d.f. = 1, $P = 0.364$).

Table 1
Number of women according to age and exposure group. Group percentages in brackets

Age group (exposed)	Exposed	Non-exposed	Total
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
40–49	142 (27.2)	129 (23.9)	271 (25.5)
50–59	222 (42.5)	219 (40.6)	441 (41.5)
60–75	158 (30.3)	192 (35.6)	350 (33.0)
Total	522	540	1062

Six exposed and three non-exposed women were lost to follow-up and excluded from subsequent analyses. The remaining cohort is 1053 women: 516 exposed and 537 non-exposed.

Table 2

Type of breast tissue component by age and exposure (age and exposure-group specific detection rates in parentheses)

	Age group (years)	Fibro-adeno	Fibro-fatty	Fatty	Total
Exposed	40–49	93 (66.4)	33 (23.6)	14 (10.0)	140
	50–59	17 (7.8)	104 (47.5)	98 (44.7)	219
	60–75	0 (0.0)	20 (12.7)	137 (87.3)	157
	Total	110	157	249	516
Non-exposed	40–49	89 (69.5)	31 (24.2)	8 (6.3)	128
	50–59	12 (5.5)	101 (46.3)	105 (48.2)	218
	60–75	0 (0.0)	39 (20.4)	152 (79.6)	191
	Total	101	171	265	537

- *Malignant changes* (primary mammographic signs of cancer such as clusters of microcalcifications, linear or radiated changes with speculated margins around a central point, density and size of the lesion, and co-existing secondary lesions) appeared in 18 exposed and 12 non-exposed women. The differences in the detection of malignant changes among women in the exposed group (3.5%) and the non-exposed (2.2%) was not significant ($\chi^2 = 1.45$, d.f. = 1, $P = 0.228$).

Following mammography, 137 women, (69 exposed and 68 non-exposed), had excisional biopsy and histological confirmation. From the exposed group, there were 11 biopsy-proved cancers, 12 discrete benign lesions and 46 biopsies of poorly defined lesions, usually some form of fibrocystic disease without a discrete mass. The corresponding numbers from the non-exposed group were 8, 14 and 46. In conclusion, eleven of the 516 (2.1%) occupationally exposed women to pesticides had findings of malignancy, compared with 8 of the 537 (1.5%) non-exposed women. The difference

between the two groups was not significant ($\chi^2 = 0.59$, d.f. = 1, $P = 0.442$).

4. Discussion

It is well known that organochlorine pesticides were used on Crete. DDT was also sprayed against malaria; its use was restricted in 1969. Crete remains an area where the use of organic pesticides is often dangerous: acute poisonings with organocarbamates and organophosphates are common [17–19].

This study of healthy women from the first outreach screening programme on Crete considers detection rates of mammographic findings, some of which are cancerous or known markers of varying risk for subsequent invasive breast cancers [20–27].

The detection rates of biopsy-proven malignant tumours of the two groups were not statistically different. However, both groups had a larger number of breast cancers in the age group 40–49 years: exposed group (6 or 4.3%), non-exposed group (3 or 2.3%). The

Table 3

Mammographic findings by age and exposure^{a,b}

Mammography findings	Age (years)						Total	
	40–49		50–59		60–75		Exp	Non-exp
	Exp	Non-exp	Exp	Non-exp	Exp	Non-exp	n (%)	n (%)
Fibrocystic changes	27	24	24	16	0	0	51 (9.9)	40 (7.4)
Ductal hyperplasia	16	12	20	8	0	0	36 (7.0)	20 (3.7)
Fibrocystic changes and ductal hyperplasia	27	18	34	14	10	8	71 (13.8)	40 (7.4)
Fibroadenoma	14	3	0	0	0	0	14 (2.7)	3 (0.6)
Inflammatory mastitis (bacteria, traumatic)	14	8	10	4	10	4	34 (6.6)	16 (3.0)
Gross cystic disease	11	12	41	29	34	21	86 (16.7)	62 (11.5)
Non-hyperplastic fibrosis and sclerosing adenosis	12	8	26	13	0	0	38 (7.4)	21 (3.9)
Lipoma	3	3	0	0	20	15	23 (4.5)	18 (3.4)
Malignant changes	3	4	7	6	8	2	18 (3.5)	12 (2.2)
Normal findings	13	36	57	128	75	141	145 (28.1)	305 (56.8)
Total	140	128	219	218	157	191	516	537

^a Exp, exposed; Non-exp, non-exposed.

^b Exposure-group specific detection rates are shown in the last two columns.

corresponding numbers and detection rates for the older women (aged 50–75 years) were 5 (1.3%) and 5 (1.2%), respectively. This is the opposite of what is expected, in particular for the exposed group, where the detection rate of breast cancer in the age group 40–49 years was significantly larger than that of the 50–75 year old age group ($\chi^2 = 4.272$, d.f. = 1, $P = 0.039$).

These results confirm, first, the value of screening for early diagnosis of breast tumours in the 40–49 year age group. Second, as all the women in the exposed group had medium to long exposure to occupationally-used pesticides (at least 10 years work in greenhouses), the link between exposure and diagnosed neoplastic disease, could probably only be identified in the younger age group.

Page and colleagues [21,23] suggest four categories of markers of varying risk for subsequent invasive breast cancer: no increased risk, slightly increased risk (1.5–2 times), moderately increased risk (4–5 times) and high risk (8–10 times). Inflammatory mastitis, lipoma, fibrocystic changes and ductal hyperplasia (without atypia) are in the ‘no increased risk’ category; fibrohyperplasia without atypia (fibrocystic changes plus ductal hyperplasia), sclerosing adenosis and gross cystic disease indicate ‘slightly increased risk’; and fibroadenoma indicates ‘moderately increased risk’.

Of the markers in the ‘no increased risk’ category, only the detection rates of ductal hyperplasia (without atypia) and inflammatory mastitis had a significant association with the exposure to pesticides. A large part of the risk for inflammatory mastitis may be due to other non-pesticide-specific factors (bacterial, nutrient deficiencies, traumatic, etc.) to which women engaged in agricultural work in or out of greenhouses are exposed.

All three markers in the ‘slightly increased risk’ category, had significant associations with occupational exposure to pesticides. Risks of detection for ‘exposed’ women were 1.85, 1.88 and 1.44 times those of ‘non-exposed’ women, respectively.

For fibroadenomas, the only ‘moderately increased risk’ marker, there was a significant association between detection and exposure to occupational pesticides; the risk for exposed women was 4.86 times that of non-exposed women.

While a rigorous analysis of the link between occupationally-used organic pesticides and the incidence of mammographic findings requires risk ratios to be adjusted for potential confounding factors, these preliminary results indicate the magnitude of the risks and their relative order. This screening programme detected more breast cancers than expected in the younger group (40–49 years) compared with the older age group (50–75 years), and this was more pronounced in the exposed group. This result confirms that early screening for breast cancer is effective and represents the best oppor-

tunity for a reduction in breast cancer mortality. Compared with the non-exposed group, exposed women also had significantly higher detection rates for a number of lesions, some of which are risk factors for subsequent invasive breast cancer. The relative risks of these lesions among women exposed to occupationally-used pesticides compared with non-exposed women were approximately 2, except for fibroadenoma where the risk was approximately 5-fold. This implies that for the exposed women, the overall risk of subsequent breast cancer may increase further.

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