



Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe.

Sara Villeneuve, Diane Cyr, Elsebeth Lynge, Laurent Orsi, Svend Sabroe, Franco Merletti, Giuseppe Gorini, Maria Morales-Suarez-Varela, Wolfgang Ahrens, Cornelia Baumgardt-Elms, et al.

► To cite this version:

Sara Villeneuve, Diane Cyr, Elsebeth Lynge, Laurent Orsi, Svend Sabroe, et al.. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe.. Occup Environ Med, 2010, 67 (12), pp.837-44. 10.1136/oem.2009.052175 . inserm-00530267

HAL Id: inserm-00530267

<https://inserm.hal.science/inserm-00530267>

Submitted on 2 Mar 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe

Sara Villeneuve¹, Diane Cyr¹, Elsebeth Lynge², Laurent Orsi¹, Svend Sabroe³, Franco Merletti⁴, Giuseppe Gorini⁵, Maria Morales-Suarez-Varela^{6,7,8}, Wolfgang Ahrens⁹, Cornelia Baumgardt-Elms¹⁰, Linda Kaerlev¹¹, Mikael Eriksson¹², Lennart Hardell¹³, Joëlle Févotte¹⁴, Pascal Guénel^{1*}

¹ CESP, Centre de recherche en épidémiologie et santé des populations INSERM : U1018, Université Paris Sud - Paris XI, Université de Versailles-Saint Quentin en Yvelines, INED, FR

² Institute of Public Health University of Copenhagen, Copenhagen, DK

³ Department of Epidemiology University of Aarhus, School of Public Health, DK

⁴ Unit of Cancer Epidemiology CERMS and Centre for Oncologic Prevention, Université de Turin, Piemonte, IT

⁵ Epidemiology and Public Health, Environmental and Occupational Epidemiology Unit ISPO Cancer Prevention and Research Institute, Florence, IT

⁶ Unit of Public Health and Environmental Care Université de Valence, Department of Preventive Medicine, ES

⁷ CB06/02/045, Centro de Investigación Biomedica en Red Institute Carlo III, CIBER actions Epidemiology and Public Health Institute Carlo III, ES

⁸ Research Foundation University Hospital Dr. Peset, Valencia, ES

⁹ Bremen Institute for Prevention Research and Social Medicine Bremen Institute for Prevention Research and Social Medicine, Bremen, DE

¹⁰ Hamburg Cancer Registry Hamburg Cancer Registry, Hamburg, DE

¹¹ Center for National Clinical Databases South Odense University Hospital, Department of Research and HTA, DK

¹² Department of Oncology Lund University Hospital, Lund, SE

¹³ Department of Oncology Orebro University Hospital, Orebro, SE

¹⁴ UMRESTTE, Unité Mixte de Recherche Epidémiologique et de Surveillance Transport Travail Environnement INRETS, INVS, Université Claude Bernard - Lyon I, 25, Avenue François Mitterrand, F-69675 BRON Cédex, FR

* Correspondence should be addressed to: Pascal Guénel <pascal.guenel@inserm.fr>

Abstract Objectives

Male breast cancer is a rare disease of largely unknown etiology. Besides genetic or hormone-related risk factors, a large number of environmental chemicals are suspected to play a role in breast cancer. The identification of occupations or occupational exposures associated with an increased incidence of breast cancer in men may help to identify mammary carcinogens in the environment.

Methods

Occupational risk factors of male breast cancer were investigated in a multi-centre case-control study conducted in 8 European countries, including 104 cases and 1901 controls. Lifetime work history was obtained during in-person interviews. Occupational exposures to endocrine disrupting chemicals (alkylphenolic compounds, phthalates, PCBs and dioxins) were assessed on a case-by-case basis from expert judgment.

Results

Male breast cancer incidence was more particularly increased in motor vehicle mechanics (OR=2.1, CI 1.0–4.4) with a dose-effect relationship with duration employment. It was also increased in paper makers and painters, and in workers in forestry and logging, health and social work, and manufacture of furniture. The odds ratio for exposure to alkylphenolic compounds above median was 3.8 (CI 1.5–9.5). This association persisted after adjustment for occupational exposures to other environmental estrogens.

Conclusion

These findings suggest that some environmental chemicals are possible mammary carcinogens. Gasoline, organic petroleum solvents or PAH can be suspected from the consistent elevated risk of male breast cancer observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer.

Author Keywords Case-Control Studies ; Occupations ; Occupational Exposures ; Breast Neoplasms, Male ; Endocrine Disruptors

INTRODUCTION

Male breast cancer is a rare disease, representing less than 1% of all breast cancers, with incidence rates of approximately 1 per 100,000 men per year in Europe.[1] Factors linked to hormonal or reproductive function in women have been studied extensively as etiologic factors in female breast cancers, but little is known about the etiology of male breast cancer. The risk factors reported for this disease include mutations of the BRCA2 gene, the presence of an extra X chromosome (Klinefelter syndrome), infertility, cryptorchidism, mumps orchitis, or alcohol drinking.[2]

Certain environmental exposures, such as organic solvents [3] or endocrine disrupting chemicals that interfere with hormonally mediated processes and can stimulate the growth of breast cancer cells in laboratory studies are also suspected risk factors for breast cancer.[4 –6] Many studies on female breast cancer risk in the community have been conducted in relation to a few endocrine disrupting chemicals such as DDT or PCBs with mainly negative results.[7 , 8] However, occupational studies on female breast cancer where exposures are higher and better characterized compared with community settings have rarely been conducted. These studies have shown associations between female breast cancer and exposure to certain organic solvents,[9 , 10] pesticides,[11 , 12] PCBs [13] or other endocrine disruptors.[14] There is also growing evidence that disruption of circadian rhythm during night shift work increases the risk of female breast cancer.[15] For the purpose of identifying mammary carcinogens in occupational settings, the study of male breast cancer offers several advantages over female breast cancer for identifying environmental mammary carcinogens, because exposures to the occupational agents of interest, such as PAHs, occur more frequently in jobs held by men than by women. In addition, confounding from female reproductive risk factors is not a concern in men. Occupational studies have inconsistently reported associations between male breast cancer and exposure to heat,[16 –19] gasoline, PAHs or combustion products,[19 , 20] and electromagnetic fields.[19 , 21 –23] None of these studies has specifically investigated the role of exposure to endocrine disrupting chemicals.

The first objective of this study was to examine the risk of male breast cancer by occupation to give possible clues about potential occupational carcinogens. A second objective was to test the hypothesis that exposure to environmental estrogens present in occupational settings [24 , 25] increased the risk of male breast cancer. More specifically, we investigated occupational exposures to alkylphenolic compounds,[14] phthalates,[26 , 27] PCBs and dioxins,[28] and pesticides.[12]

MATERIAL AND METHODS

We conducted a European multi-centre case-control study for 7 sites of rare cancers including male breast (gallbladder and extra-hepatic bile ducts, small intestine, bone, eye melanoma, thymus and mycosis fungoides). Cases and controls were recruited in selected areas of 8 European countries. The recruitment was population-based in Denmark, France, Germany, Italy and Sweden, and hospital-based in Latvia, Portugal and Spain. Findings on alcohol drinking in relation to male breast cancer have been reported previously for the countries that used a population-based design.[29] The study design and the procedures of data collection have been described in detail earlier [30] and are summarized below.

Recruitment of cases and controls

Cases were men living in the participating study areas who were diagnosed with a breast cancer between January 1st, 1995 and June 30th, 1997. Only men aged 35–70 years at diagnosis were eligible for the study. Inclusion was restricted to this age range because the study focused on occupations and because occupational exposures that occurred in early periods among older subjects may be hard to recall, and difficult to assess by study investigators due to changes in work processes. Case ascertainment was based on regular contacts with clinical and pathology departments in each study area. For each case an expert pathologist reviewed the pathology report and one slide representative of the tumor. In total 122 male breast cancer patients were eligible for the study. Eighteen cases could not be contacted because the doctor did not give permission or the patient refused to participate. In total 104 cases (85%) were interviewed and were available for the analysis (table 1).

Controls were selected randomly during case recruitment and were frequency-matched to the cases by year of birth (5-year strata), sex, and study area. Controls were selected from population registers in Denmark, Italy and Sweden, from electoral rolls in France and from municipality registers in Germany. Colon cancer patients were regarded as appropriate alternatives to population controls in some cases, as no occupational exposure to chemicals is known to play a role in colon cancer. Hospital-based cancer controls were selected randomly among incident colon cancer patients in Latvia and Spain, and among the colon and a few stomach cancer patients in Portugal. The controls served as a common pool of controls for each of the seven groups of rare cancer cases included in the European study. For the present study we selected only control men in the study areas where at least one male breast cancer patient was included. The participation rate among population controls was high in France (81%) and Italy (74%) but it was lower (<60%) in Denmark, Germany, and Sweden. In countries using a hospital-based design, the participation rate among cancer controls was above 95%. The overall participation rate in controls was 67%, and 1901 controls were available for the analysis (table 1).

Data collection

A structured questionnaire was first developed in English, translated into the language of each participating country and then back-translated into English for quality control. This questionnaire was used during a face to face or a telephone (Denmark, Sweden) interview by a trained interviewer. We obtained information on socio-demographic characteristics, previous medical conditions, lifestyle factors, anthropometric characteristics, alcohol and tobacco consumption. A detailed occupational questionnaire was used for each job held for more than 6 consecutive months during lifetime. Questionnaires specific to 27 work tasks such as welding or painting were also used whenever relevant to search for particular occupational exposures.

Coding of jobs and occupational exposures

Each job held for more than 6 month was coded for occupation and industry by trained coders. Occupation was coded according to the International Standard Classification of Occupation (ISCO) of the International Labor Office, 1968 revision. Industry was coded according to the Classification of Activities in the European Community (NACE), 1996 revision.

Exposure to endocrine disrupting chemicals was assessed for each job held during the subjects' work history by an expert in occupational hygiene. Exposure assessment was conducted by individually reviewing the job-specific questionnaires to collect information on the production of the plant, the work tasks performed, or the type of equipment and chemical products used by the worker. In order to decrease the total number of jobs to be reviewed by the expert, we made a preliminary selection of the job questionnaires based on their ISCO and NACE codes and discarded the jobs where exposure to endocrine disrupting chemicals had no chance to occur. Based on the expert's judgment and a literature review, exposure to alkylphenolic compounds, phthalates, PCBs and dioxins was coded using semi-quantitative indicators for exposure probability (0: not exposed; 1: possibly exposed; 2: probably exposed; 3: certainly exposed), exposure frequency (1: < 30% of working hours; 2: 30–70%; 3: > 70%) and exposure intensity, based on the expert judgment about airborne concentration or dermal contact (1: low; 2: medium; 3: high). Coding of exposure was blind as to case-control status. Exposure to pesticides was assessed in the same way, but a detailed assessment by type of pesticide was beyond the scope of the present paper.

We calculated an exposure score for each job in the subject's work history as the product of exposure probability, frequency and intensity and the duration of the job period in years. The lifetime cumulative exposure of each study subject consisted of the sum of the job-specific exposure scores over the entire work history.

Statistical analysis

Odds ratios were calculated for workers ever employed in an occupation or industry using workers who were never employed in that occupation or industry as a reference group. Occupations and industries were defined by the 2- or 3- digit level of the ISCO code and by the 2-digit level of the NACE code, respectively. Only job groups with at least 5 cases are presented.

In the analyses by occupational exposure to endocrine disrupting chemicals, we categorized ever-exposed subjects into 2 groups according to the median of the cumulative exposure distribution among controls, and used never exposed subjects as the reference category. For pesticides, exposed workers were divided according to exposure tertiles.

All analyses were conducted using unconditional logistic regressions using the SAS® software package (version 9, Cary, NC). Odds ratios were adjusted for age (5-year age group) and country, the stratification variables, as well as for potential confounders coded as categorical variables, including alcohol drinking, body mass index and education.

We also conducted several rounds of analyses (i) restricting to countries that used a population-based design and no colon cancer controls; (ii) restricting to the cases with known estrogen positive receptor status (48 out of 54 cases with known status); and for the occupational exposure analyses (iii) calculating cumulative exposure scores with a lag time of 5, 10, or 15 before diagnosis or interview for the controls; (iv) excluding jobs with low exposure probability from the cumulative exposure scores. These sensitivity analyses did not modify our findings and are not shown.

RESULTS

Study sample

The distribution of cases and controls by age, alcohol consumption, and education are presented in Table 2. The age distribution of cases and controls did not differ significantly. As reported earlier, alcohol consumption was strongly associated with male breast cancer.[29] Lower education was associated with some increase in risk, although the odds ratios did not reach statistical significance. No statistically significant excess risk was observed in any BMI category. Because BMI was weakly associated with male breast cancer in some countries,[29] we adjusted for this variable in further analyses.

Occupations and industries

Odds ratios for male breast cancer were increased in wood preparation workers and paper makers (OR=2.4, CI 0.9–6.5), motor vehicle mechanics (OR=2.1, CI 1.0–4.4), and painters (OR=2.3, CI 1.0–5.2) (table 3). The odds ratio increased markedly for workers employed for 10 or more years as motor vehicle mechanics (OR=5.9, CI 2.4–14.6) (not shown). Conversely, a non-significantly decreased odds ratio was observed for farmers and agricultural workers.

Table 4 presents odds ratios associated with specific industries. Increased odds ratios were observed in forestry and logging (OR=2.4, CI 1.0–5.6), health and social work (OR=2.3, CI 1.1–5.1), and sale and repair of motor vehicles (OR=1.8, CI 1.0–3.2). This later increase (NACE 50) was explained by the increased odds ratio in motor vehicle mechanics (ISCO 8–43), with 9 cases and 57 controls being classified in both NACE 50 and ISCO 8–43. Odds ratios in the manufacture of rubber and plastic (OR=1.9, CI 0.8–4.6), manufacture of electrical machinery (OR=2.0, CI 0.8–5.3), and manufacture of furniture (OR=1.8, CI 0.9–3.7), were also increased but did not reach the level of statistical significance.

Occupational exposures

In table 5 , the odds ratio adjusted for non-occupational risk factors was elevated for alkylphenolic compounds above median (OR_a=3.8, CI 1.5–9.5), and a dose-response trend was apparent ($p<0.01$). The odds ratio for exposure to PCBs and dioxin above the median was also increased (OR_b=2.1, CI 1.0–4.5) and at the limit of statistical significance. When adjusting further for exposures to other endocrine disruptors (OR_b in table 5), i.e. including all occupational exposure variables in a single model, male breast cancer incidence remained associated with alkylphenolic compounds (OR=3.3, CI 1.1–9.9 exposure above median), but the dose-response trend was not statistically significant. No increased risk was observed for phthalates, and for PCBs and dioxins. Exposure to pesticides was not associated with male breast cancer in either model. Confounding between occupational exposures is thus apparent from table 5 , indicating that multiple exposures to endocrine disruptors occurred among workers in our data.

DISCUSSION

We found that the incidence of male breast cancer was increased in wood preparation workers and paper makers, in motor vehicle mechanics, and in painters as well as in workers in the industry of forestry and logging, in health and social work, in the manufacture of furniture, and in sale and repair of motor vehicles. We also investigated occupational exposures to endocrine disrupting chemicals, and found that male breast cancer incidence was more particularly associated with alkylphenolic compounds.

Study strengths and limitations

This is a relatively large study on male breast cancer conducted in 8 European countries. Despite the large study base, the high participation rate among male breast cancer patients [30] and the large number of controls, some analyses were based on relatively low statistical power. We calculated for example that a 2-fold increased odds ratio was detectable with a statistical power of 80% ($\alpha=5\%$, two-sided) if the exposure prevalence among control was at least 15%, a condition that was not met in all calculations. Chance findings due to multiple testing are also possible. Nevertheless, if the observed associations are real, they may have been difficult to detect in epidemiological studies on female breast cancer based on higher numbers of cases but much lower exposure prevalence.

The overall participation rate among controls was 67%, with large disparities across countries. A selection bias, e.g. according to socioeconomic status or education, was thus possible, but should be controlled for, at least in part, by adjusting for education. Restricting to countries with high participation rates among controls such as France and Italy did not alter the findings, giving reassurance that selection bias does not constitute a major problem.

Using colon cancer controls in countries with a hospital-based design could have biased our results if colon cancer was associated with the occupational risk factors of interest. However, with the exception of low physical activity,[31] there is no recognized occupational risk factor for colon cancer. Our results were unchanged when the analyses were conducted separately in countries that did not use colon cancer controls.

Occupational exposures to estrogenic chemicals were assessed by expert judgment reviewing the job-specific questionnaires blindly as to the case-control status. This case-by-case exposure assessment method may lead to non-differential exposure misclassification errors, but it is considered as more efficient than a job-exposure matrix, since the exposure is evaluated for individual workers rather than for groups of workers with the same job.[32] Exposures to estrogenic chemicals arising from the general environment could not be evaluated in our study. This should not be a major problem considering that environmental exposures occur at lower levels than in occupational settings, and that they should be equally distributed among occupationally and non-occupationally exposed subjects.

Occupations and industries

Few studies have investigated male breast cancer risk in relation to occupational risk factors, but most of them have several drawbacks, including low statistical power,[16 –18] the use of a mortality rather than incidence register to recruit male breast cancer patients,[19] or information on occupation known from census data at only one point in time instead of lifetime occupational history.[20 , 23 , 33]

We found a 2-fold increased incidence of male breast cancer in motor vehicle mechanics, with an indication of a dose-response relationship with duration of employment (OR= 5.9 in men employed for 10 or more years in that occupation). Similarly, a registry-based case-control study in Denmark [20] reported an increased incidence of male breast cancer in workers employed in service stations, vehicle maintenance, wholesale trade of gasoline, or car repair shops. Exposure to solvents, gasoline and vehicle combustion products, containing suspected mammary carcinogens such as benzene and polycyclic aromatic hydrocarbons (PAH) may be causal explanations for these associations,[3 , 34] and previous studies on female breast cancer provided some evidence of a link with exposure to solvents.[9 , 10] This link is of interest and needs to be investigated further in male and in female breast cancer.

We reported an increased incidence of male breast cancer in painters (OR=2.3, CI 1.0–5.3) suggesting a potential adverse effect of solvents again, or paint additives. The elevated incidence in wood preparation workers and paper makers, and in men employed in forestry and logging, also suggests that chemicals with endocrine disrupting properties, such as volatile organic compounds in wood,[35] could play a role in breast cancer.

Conversely, no increased incidence of male breast cancer was detected in our study among metal processors (ISCO 7-2, table 3) or among men employed in the metal manufacturing industry (NACE 27, table 4). These findings do not confirm the elevated risks of male breast cancer reported in workers employed in blast furnaces, steel work and rolling mills,[16 –19] and hence do not support the hypothesis that exposure to heat [36] which is common in these industries, may be carcinogenic to the breast. Our results do not point either toward a role of electromagnetic fields in male breast cancer, as suggested by other investigators,[21 , 37 , 38] since occupations with potentially high exposures such as electricians or welders were not at increased risk in our data.

Occupational exposures to endocrine disrupting chemicals

This is the first study examining a possible association between male breast cancer and exposure to endocrine disrupting chemicals. Many hormonally active compounds suspected to affect breast cancer due to their estrogenic or anti-estrogenic properties were identified in laboratory studies [39], but only a few have been investigated in epidemiological studies. We examined estrogenic compounds that can be found in occupational settings,[24 , 25] and excluded chemicals with very low exposure prevalence in the study such as bisphenol A or parabens.

Exposure to alkylphenolic compounds was associated with male breast cancer in our data. Alkylphenol polyethoxylates surfactants and alkylphenols are used in a broad range of occupations and industries, but are mainly used as detergents, in plastics, rubber products or in cosmetics,[24 , 25] and in the textile industry.[40] The workers exposed to alkylphenolic compounds in the present study can be better characterized by their industry, and were mainly employed in finishing of textiles, in the manufacture of leather clothes, in the industry of pulp and paper, plastics, paints and varnishes, soap and detergents, and rubber products. To our knowledge, only one study in women has examined the relation between exposure to alkylphenolic compound and breast cancer.[14] In this population-based case-control study, the possibility of exposure to 18 xenoestrogens was determined using a job-exposure matrix derived from the US National Occupational Exposure Survey database. Probable exposure to 4-octylphenol, an alkylphenolic compound, was associated with an odds ratio of 2.9 (0.8–10.8) after adjustment for potential confounders. Overall, our findings provide some support to the hypothesis that alkylphenolic compounds may play a role in breast cancer incidence. It should be noted however that multiple exposures to endocrine disruptors occurred in our data, and that confounding made it difficult to disentangle the effects of individual compounds. It is thus possible that the main association observed between male breast cancer and alkylphenolic compounds should be accounted for multiple exposure to different classes of estrogenic compounds, which can have synergistic effects.[41]

The odds ratio associated with exposure to dioxins and PCBs above median was increased 2-fold, although this association was not apparent after adjusting for alkylphenolic compounds. PCBs and dioxins are two groups of persistent organochlorine compounds. PCBs were used as dielectric fluids in electrical capacitors, but also for miscellaneous uses in adhesives, oils or paint [28]. Most studies on the association between breast cancer and environmental exposure to PCBs, based on measurements in the blood or fat of cases or controls, reported no increased risk of female breast cancer.[8] In a cohort study of women employed in capacitor facilities, no overall increase of breast cancer incidence was detected after exposure to PCBs, as estimated from a job-exposure matrix.[13] Several studies, however, point to a possible role of PCBs in breast cancer for the subgroup of potentially predisposed women who carry a genetic variant in the CYP1A1 gene.[42 –45] There also remain uncertainties concerning the role of certain PCB subgroups, such as dioxin-like PCBs.[8] Dioxins have been investigated less frequently in relation to breast cancer. In the cohort of women exposed to 2,3,7,8-TCDD - the main dioxin - following the explosion of a trichlorophenol manufacturing plant near Seveso, Italy, an increase in female breast cancer incidence was observed in the most contaminated areas [46] and among women with higher TCDD serum levels.[47] Increased mortality from breast

cancer in both women and men was also reported in an international cohort of workers exposed to phenoxy herbicides contaminated with dioxins.[48] Overall these data provide some support to the hypothesis that some PCBs and dioxins may increase the risk of breast cancer, and requires further attention.

Phthalates have been widely used as plasticizers in soft plastics or in cosmetics,[49] but they have never been investigated thoroughly in relation to breast cancer incidence in an epidemiological study. We found no significant association of male breast cancer with exposure to phthalates possibly because of confounding by alkylphenolic compounds. Because of their widespread use, their effects in hormone-related cancers would deserve further attention. The role of environmental exposures to persistent organochlorine pesticides, such as DDT, was investigated in many studies with mainly negative findings[7]. Other studies in female farmers reported increased breast cancer risk in women likely exposed to pesticides.[11] or living closer to pesticide application areas.[12] Our data provide no support for an association between pesticide exposure and breast cancer in men, but the lack of information on specific pesticides may account for these negative findings.

Conclusion

The elevated risk of male breast cancer in certain occupations provided some clues about possible environmental mammary carcinogens. The elevated risk of male breast cancer among motor vehicle mechanics, points to a role of PAH and gasoline or petroleum solvents in breast carcinogenesis, that needs to be investigated further in studies of male or female breast cancer. For the first time in male breast cancer, we have shown that endocrine disrupting chemicals could affect breast cancer risk. These results support the growing evidence that breast cancer may be linked to exposure to environmental pollutants and should encourage further studies on this issue.

Acknowledgements:

The European Study Group on Occupational Causes of Rare Cancers: DENMARK: Herman Autrup, Henrik Kolstad, Linda Kaerlev, Elsebeth Lynge, Jørn Olsen, Lisbeth Norum Pedersen, Svend Sabroe, Preben Johansen, Stein Poulsen, Peter Stubbe Teglbaerg, Mogens Vyberg. FRANCE: Pascal Guénel, Joëlle Févotte, Diane Cyr and the members of the FRANCIM association: Patrick Arveux, Antoine Buemi, Paule-Marie Carli, Gilles Chaplain, Jean-Pierre Daurès, Jean Faivre, Pascale Grosclaude, Anne-Valérie Guizard, Michel Henry-Amar, Guy Launoy, François Ménégoz, Nicole Raverdy, Paul Schaeffer. GERMANY: Wolfgang Ahrens, Cornelia Baumgardt-Elms, Sibylle Gotthardt, Ingeborg Jahn, Karl-Heinz Jöckel, Hiltrud Merzenich, Andreas Stang, Christa Stegmaier, Antje Timmer, Hartwig Ziegler. ITALY: Terri Ballard, Franco Bertoni, Giuseppe Gorini, Sandra Gostinicchi, Giovanna Masala, Enzo Merler, Franco Merletti, Lorenzo Simonato, Paola Zambon. LATVIA: Irena Rogovska, Galina Sharkova, Aivars Stengrevics. LITHUANIA: Jolita Gibaviciene, Laimonas Jazukevicius, Juozas Kurtinaitis, Poma Pociute. PORTUGAL: Noemia Alfonso, Altamiro Costa-Pereira, Sonia Doria, Carlos Lopes, José Manuel Lopes, Ana Miranda, Cristina Santos. SPAIN: M Adela Sanz Aguado, Juan J Aurrekoetxea, Concepción Brun, Alicia Córdoba, Miguel Angel Martínez González, Francisco Guillén Grima, Rosa Guarch, Agustín Llopis González, Blanca Marín, Amparo Marquina, María M Morales Suárez-Varela, Inés Aguinaga Ontoso, JM Martínez Peñuela, Ana Puras, Francisco Vega, Maria Aurora Villanueva Guardia. SWEDEN: Mikael Eriksson, Lennart Hardell, Irene Larsson, Hakan Olson, Monica Sandström, Gun Wingren. SWITZERLAND: Jean-Michel Lutz. UNITED KINGDOM: Janine Bell, Ian Cree, Tony Fletcher, Alex JE Foss.

Funding: The study "Occupational risk factors for rare cancers of unknown etiology" was financially supported by the European Commission, DGXII, grants no BMH1 CT 931630 and ERB CIPD CT 940285, and national funding agencies. Denmark: The Strategic Environment Programme. France: Ligue Nationale contre le Cancer, Fondation de France (grant No 955368), Institut National de la Santé et de la Recherche Médicale (INSERM) (grant "Réseau en Santé Publique"), French Ministry for Environment. Germany: Federal Ministry for Education, Science, Research and Technology (BMBF), grant no. 01-HP-684/8. Italy: MURST, Region Piedmont, Ministry of Labour, Italian Association for Cancer Research, Compagnia SanPaolo/FIRMS. Portugal: Junta Nacional de Investigação Científica e Tecnológica, Praxis XXI, no2/2.1/SAU/1178/95. Spain: Fondo de Investigación de la Sanitaria, Ministerio de Sanidad y Consumo, Unidad de Investigación Clínico-Epidemiológica, Hospital Dr. Peset. Generalitat Valenciana; Departamento de Sanidad y Consumo, Gobierno Vasco; Fondo de Investigación de la Sanitaria (FIS), Ministerio de Sanidad y Consumo, Ayuda a la Investigación del Departamento de Salud del Gobierno de Navarra. Sweden: Swedish Council for Work Life Research, Research Foundation of the Department of Oncology in Umeå, Swedish Society of Medicine, Lund University Hospital Research Foundation, Gunnar, Arvid and Elisabeth Nilsson Cancer Foundation, Örebro County Council Research Committee, Örebro Medical Center Research Foundation, John and Augusta Persson Foundation for Scientific Medical research, Berta Kamprad Foundation for Cancer Research.

Footnotes:

Competing interests : All authors declare they have no potential competing financial interest

References:

- 1 . Curado MP , Edwards B , Shin HR . Cancer Incidence in Five Continents . IX : Lyon International Agency for Research on Cancer ; 2008 ;
- 2 . Weiss JR , Moysich KB , Swede H . Epidemiology of male breast cancer . Cancer Epidemiol Biomarkers Prev . 2005 ; 14 : (1) 20 - 26
- 3 . Labreche FP , Goldberg MS . Exposure to organic solvents and breast cancer in women: a hypothesis . American Journal of Industrial Medicine . 1997 ; 32 : (1) 1 - 14
- 4 . Soto AM , Sonnenschein C , Chung KL . The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants . Environ Health Perspect . 1995 ; 103 : (Suppl 7) 113 - 22

- 5 . Brody JG , Moysich KB , Humblet O . Environmental pollutants and breast cancer: epidemiologic studies . *Cancer* . 2007 ; 109 : (12 Suppl) 2667 - 711
- 6 . Dey S , Soliman AS , Merajver SD . Xenoestrogens may be the cause of high and increasing rates of hormone receptor positive breast cancer in the world . *Medical Hypotheses* . 2009 ; 72 : (6) 652 - 56
- 7 . Lopez-Cervantes M , Torres-Sanchez L , Tobias A . Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence . *Environmental Health Perspectives* . 2004 ; 112 : (2) 207 - 14
- 8 . Negri E , Bosetti C , Fattore E . Environmental exposure to polychlorinated biphenyls (PCBs) and breast cancer: a systematic review of the epidemiological evidence . *Eur J Cancer Prev* . 2003 ; 12 : (6) 509 - 16
- 9 . Petralia SA , Chow WH , McLaughlin J . Occupational risk factors for breast cancer among women in Shanghai . *American Journal of Industrial Medicine* . 1998 ; 34 : (5) 477 - 83
- 10 . Peplonska B , Stewart P , Szeszenia-Dabrowska N . Occupational exposure to organic solvents and breast cancer in women . *Occup Environ Med* . 2009 ;
- 11 . Duell EJ , Millikan RC , Savitz DA . A population-based case-control study of farming and breast cancer in North Carolina . *Epidemiology* . 2000 ; 11 : (5) 523 - 31
- 12 . Engel LS , Hill DA , Hoppin JA . Pesticide use and breast cancer risk among farmers' wives in the agricultural health study . *American Journal of Epidemiology* . 2005 ; 161 : (2) 121 - 35
- 13 . Silver SR , Whelan EA , Deddens JA . Occupational exposure to polychlorinated biphenyls and risk of breast cancer . *Environ Health Perspect* . 2009 ; 117 : (2) 276 - 82
- 14 . Aschengrau A , Coogan PF , Quinn M . Occupational exposure to estrogenic chemicals and the occurrence of breast cancer: an exploratory analysis . *American Journal of Industrial Medicine* . 1998 ; 34 : (1) 6 - 14
- 15 . Stevens RG . Light-at-night, circadian disruption and breast cancer: assessment of existing evidence . *International Journal of Epidemiology* . 2009 ; 38 : (4) 963 - 70
- 16 . Lenfant-Pejovic MH , Mlika-Cabanne N , Bouchardy C . Risk factors for male breast cancer: a Franco-Swiss case-control study . *International Journal of Cancer* . 1990 ; 45 : (4) 661 - 65
- 17 . Mabuchi K , Bross DS , Kessler II . Risk factors for male breast cancer . *Journal of the National Cancer Institute* . 1985 ; 74 : (2) 371 - 75
- 18 . Rosenbaum PF , Vena JE , Zielezny MA . Occupational Exposures Associated with Male Breast Cancer . *American Journal of Epidemiology* . 1994 ; 139 : 30 - 36
- 19 . Cocco P , Figgs L , Dosemeci M . Case-control study of occupational exposures and male breast cancer . *Occupational and Environmental Medicine* . 1998 ; 55 : (9) 599 - 604
- 20 . Hansen J . Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products . *American Journal of Industrial Medicine* . 2000 ; 37 : (4) 349 - 52
- 21 . Demers PA , Thomas DB , Rosenblatt KA . Occupational exposure to electromagnetic fields and breast cancer in men . *American Journal of Epidemiology* . 1991 ; 134 : (4) 340 - 47
- 22 . Stenlund C , Floderus B . Occupational exposure to magnetic fields in relation to male breast cancer and testicular cancer: a Swedish case-control study . *Cancer Causes & Control* . 1997 ; 8 : (2) 184 - 91
- 23 . Pollan M , Gustavsson P , Floderus B . Breast cancer, occupation, and exposure to electromagnetic fields among Swedish men . *American Journal of Industrial Medicine* . 2001 ; 39 : (3) 276 - 85
- 24 . van Tongeren M , Nieuwenhuijsen MJ , Gardiner K . A Job-Exposure Matrix for Potential Endocrine-disrupting Chemicals Developed for a Study into the Association between Maternal Occupational Exposure and Hypospadias . *Annals of Occupational Hygiene* . 2002 ; 46 : (5) 465 - 77
- 25 . Brouwers MM , MvT , Hirst AA . Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix . *Occupational and Environmental Medicine* . 2009 ; 66 : (9) 607 - 14
- 26 . Hines CJ , Hopf NBN , Deddens JA . Estimated daily intake of phthalates in occupationally exposed groups . *J Expos Sci Environ Epidemiol* . 2009 ;
- 27 . Hines CJ , Nilsen Hopf NB , Deddens JA . Urinary Phthalate Metabolite Concentrations among Workers in Selected Industries: A Pilot Biomonitoring Study . *Ann Occup Hyg* . 2009 ; 53 : (1) 1 - 17
- 28 . Broadhurst MG . Use and replaceability of polychlorinated biphenyls . *Environmental Health Perspectives* . 1972 ; 2 : 81 - 102
- 29 . Guenel P , Cyr D , Sabroe S . Alcohol drinking may increase risk of breast cancer in men: a European population-based case-control study . *Cancer Causes Control* . 2004 ; 15 : (6) 571 - 80
- 30 . Lynge E , Afonso N , Kaerlev L . European multi-centre case-control study on risk factors for rare cancers of unknown aetiology . *European Journal of Cancer* . 2005 ; 41 : (4) 601 - 12
- 31 . Chow WH , Malmer HS , Hsing AW . Occupational risks for colon cancer in Sweden . *J Occup Med* . 1994 ; 36 : (6) 647 - 51
- 32 . Siemiatycki J , Dewar R , Richardson L . Costs and statistical power associated with five methods of collecting occupation exposure information for population-based case-control studies . *Am J Epidemiol* . 1989 ; 130 : (6) 1236 - 46
- 33 . McLaughlin JK , Malmer HSR , Blot WJ . Occupational risks for male breast cancer in Sweden . *British Journal of Industrial Medicine* . 1988 ; 45 : 275 - 76
- 34 . Rudel RA , Attfield KR , Schifano JN . Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention . *Cancer* . 2007 ; 109 : (12 Suppl) 2635 - 66
- 35 . Mellanen P , Petanen T , Lehtimäki J . Wood-Derived Estrogens: Studies in Vitro with Breast Cancer Cell Lines and in Vivo in Trout . *Toxicology and Applied Pharmacology* . 1996 ; 136 : (2) 381 - 88
- 36 . Thomas DB , Jimenez LM , McTiernan A . Breast Cancer in Men - Risk Factors with Hormonal Implications . *American Journal of Epidemiology* . 1992 ; 135 : 734 - 48
- 37 . Tynes T , Andersen A . Electromagnetic Fields and Male Breast Cancer . *Lancet* . 1990 ; 336 : 1596 -
- 38 . Matanoski GM , Breyse PN , Elliott EA . Electromagnetic Field Exposure and Male Breast Cancer . *Lancet* . 1991 ; 337 : 737 - 37
- 39 . Brody JG , Rudel RA . Environmental pollutants and breast cancer . *Environmental Health Perspectives* . 2003 ; 111 : (8) 1007 - 19
- 40 . Chen ML , Lee WP , Chung HY . Biomonitoring of alkylphenols exposure for textile and housekeeping workers . *Intern J Environ Anal Chem* . 2005 ; 85 : (4-5) 335 - 37
- 41 . Diamanti-Kandarakis E , Bourguignon JP , Giudice LC . Endocrine-disrupting chemicals: an Endocrine Society scientific statement . *Endocr Rev* . 2009 ; 30 : (4) 293 - 342
- 42 . Laden F , Ishibe N , Hankinson SE . Polychlorinated Biphenyls, Cytochrome P450 1A1, and Breast Cancer Risk in the Nurses' Health Study . *Cancer Epidemiology Biomarkers and Prevention* . 2002 ; 11 : (12) 1560 - 65
- 43 . Li Y , Millikan RC , Bell DA . Polychlorinated biphenyls, cytochrome P450 1A1 (CYP1A1) polymorphisms, and breast cancer risk among African American women and white women in North Carolina: a population-based case-control study . *Breast Cancer Research* . 2005 ; 7 : (1) R12 - R18
- 44 . Moysich KB , Shields PG , Freudenheim JL . Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk . *Cancer Epidemiology Biomarkers and Prevention* . 1999 ; 8 : (1) 41 - 44
- 45 . Zhang Y , Wise JP , Holford TR . Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut women . *American Journal of Epidemiology* . 2004 ; 160 : (12) 1177 - 83
- 46 . Pesatori AC , Consonni D , Rubagotti M . Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up . *Environ Health* . 2009 ; 8 : 39 -
- 47 . Warner M , Eskenazi B , Mocarelli P . Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study . *Environmental Health Perspectives* . 2002 ; 110 : (7) 625 - 28
- 48 . Kogevinas M , Saracci R , Winkelmann R . Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins . *Cancer Causes & Control* . 1993 ; 4 : (6) 547 - 53
- 49 . Rudel RA , Perovich LJ . Endocrine disrupting chemicals in indoor and outdoor air . *Atmos Environ* . 2009 ; 43 : (1) 170 - 81

Table 1

Number of men eligible for the study and number of respondents by country – European study on male breast cancer

	Cases			Controls		
	Interviewed	Eligible	% interviewed	Interviewed	Eligible	% interviewed
Population-based design						
Denmark	8	12	67%	195	457	43%
France	29	30	97%	308	382	81%
Germany	10	13	77%	542	972	56%
Italy	20	20	100%	210	284	74%
Sweden	7	10	70%	140	245	57%
Hospital-based design						
Latvia	3	4	75%	69	69	100%
Portugal	8	11	73%	72	75	96%
Spain	19	22	86%	365	366	100%
Total	104	122	85%	1901	2850	67%

Table 2

Comparison of cases and controls for selected characteristics – European study on male breast cancer

	cases		controls		OR [*]	95% CI
	N=104	%	N=1901	%		
Age						
<40	6	5.8	218	11.5		
40–44	6	5.8	193	10.2		
45–49	10	9.6	190	10		
50–54	14	13.5	202	10.6		
55–59	16	15.4	264	13.9		
60–64	20	19.2	329	17.3		
≥65	32	30.8	505	26.6		
Alcohol consumption (g/day)						
0–30	43	41.3	1130	59.4	1.0	Reference
>30–60	31	29.8	503	26.5	1.3	[0.8;2.2]
>60	30	28.8	268	14.1	2.6	[1.5;4.4]
Education						
Left school at age 18 or before	63	60.6	866	45.6	1.5	[0.8;2.8]
Professional training	25	24	515	27.1	1.5	[0.8;2.9]
University	16	15.4	516	27.1	1.0	Reference
Body Mass Index (kg/m ²)						
<18.5	8	7.7	83	4.4	2.0	[0.9;4.7]
18.5–25	40	38.5	733	38.6	1.0	Reference
25–30	40	38.5	883	46.4	0.8	[0.5;1.3]
>30	16	15.4	202	10.6	1.5	[0.8;2.7]

* OR adjusted for age and country

Table 3Odds ratios ^{*} by occupation (ISCO codes[†]) – European study on male breast cancer

Ever employed as	ISCO	Cases N=104	Controls N=1901	OR	95% CI
Architects, engineers	0-2/0-3	7	153	0.9	[0.4;2.1]
Administrators and managers	2-0/2-1	7	161	0.9	[0.4;1.9]
Clerical and related workers NEC [‡]	3-9	9	174	0.8	[0.4;1.6]
Salesmen, shop assistants	4-5	7	186	0.6	[0.3;1.4]
Cooks, waiters, bartenders	5-3	7	77	1.5	[0.7;3.3]
Protective service workers	5-8	6	63	1.7	[0.7;4.0]
Farmers	6-0/6-1	7	118	0.7	[0.3;1.5]
Agricultural and animal husbandry w.	6-2	17	278	0.8	[0.5;1.4]
Metal processors	7-2	6	91	1.1	[0.4;2.5]
Wood preparation workers, paper makers	7-3	5	26	2.4	[0.9;6.5]
Food and beverage processors	7-7	6	96	1.0	[0.4;2.3]
Cabinet makers	8-1	5	75	1.1	[0.4;2.7]
Blacksmiths, toolmakers, machine-tool op.	8-3	14	218	1.1	[0.6;1.9]
Machinery fitters, machine assemblers	8-41	5	73	1.2	[0.5;3.1]
Motor vehicle mechanics	8-43	9	74	2.1	[1.0;4.4]
Machinery fitters, machine assemblers NEC	8-49	6	139	0.7	[0.3;1.7]
Electricians	8-5	8	178	0.9	[0.4;1.9]
Plumbers and pipe fitters	8-71	6	55	2.0	[0.8;4.8]
Welders and flame cutters	8-72	6	65	1.4	[0.6;3.4]
Painters	9-3	7	54	2.3	[1.0;5.2]
Bricklayers, carpenters, construction workers	9-5	8	177	0.8	[0.4;1.4]
Material handling op., dockers	9-7	16	193	1.4	[0.8;2.3]
Transport equipment operators	9-8	15	288	0.9	[0.5;1.6]
Laborers NEC	9-9	11	143	1.1	[0.6;2.1]

^{*} Odds ratios are adjusted for age, country, alcohol consumption, body mass index and education[†] International Standard Classification of Occupation (ISCO) of the International Labor Office, 1968 revision[‡] NEC: not elsewhere classified

Table 4Odds ratios ^{*} by industry (NACE code[†]) – European study on male breast cancer

Ever employed in	NACE	Cases N=104	Controls N=1901	OR	95%CI
Agriculture and related activities	01	24	363	0.9	[0.6;1.4]
Forestry, logging	02	7	39	2.4	[1.0;5.6]
Manufacture of food and beverages	15	5	158	0.5	[0.2;1.3]
Manufacture of rubber and plastic	25	6	54	1.9	[0.8;4.6]
Manuf. other non-metallic mineral products	26	5	90	0.9	[0.4;2.4]
Manufacture of basic metals	27	6	130	1.1	[0.5;2.5]
Manuf. of metal products excl. machines	28	10	194	0.9	[0.5;1.7]
Manufacture of machinery and equipment	29	14	195	1.3	[0.7;2.2]
Manufacture of electrical machinery	31	5	53	2.0	[0.8;5.3]
Manufacture of other transport equipment	35	5	95	1.3	[0.5;3.2]
Manufacture of furniture	36	9	80	1.8	[0.9;3.7]
Construction	45	29	497	1.0	[0.7;1.5]
Sale and repair of motor vehicle	50	13	122	1.8	[1.0;3.2]
Wholesale trade and commission trade	51	8	186	0.8	[0.4;1.7]
Retail trade; repair of household goods	52	14	275	0.9	[0.5;1.5]
Hotels and restaurants	55	5	98	0.9	[0.4;2.3]
Land transport	60	9	156	1.0	[0.5;2.0]
Supporting transport activities	63	5	78	1.3	[0.5;3.3]
Other business activities	74	8	119	1.2	[0.6;2.5]
Public administration and defense	75	18	368	1.2	[0.7;1.9]
Health and social work	85	8	93	2.3	[1.1;5.1]
Recreational, cultural & sporting activities	92	5	64	1.6	[0.6;4.2]

^{*} Odds ratios are adjusted for age, country, alcohol consumption, body mass index and education[†] Classification of Activities in the European Community (NACE: Nomenclature des Activités dans la Communauté Européenne), 1996 revision.

Table 5

Odds ratios associated with occupational exposure to environmental estrogens. European study on male breast cancer

	Cumulative exposure scores	cases N=104	controls N=1901	ORa [*]	95% CI	P _{trend}	ORb [†]	95% CI	P _{trend}
Alkylphenolic compounds	Not exposed	94	1845	1.0	reference		1.0	reference	
	< median	3	26	1.7	[0.5;6.1]		1.3	[0.3;6.0]	
	≥ median	7	26	3.8	[1.5;9.5]	0.01	3.3	[1.1;9.9]	0.11
Phthalates	Not exposed	98	1848		reference			reference	
	< median	3	23	2.9	[0.8;10.4]		2.3	[0.5;9.7]	
	≥ median	3	26	1.7	[0.5;6.2]	0.20	0.8	[0.2;3.7]	0.51
PCB and dioxins	Not exposed	91	1722		reference			reference	
	< median	4	87	0.9	[0.3;2.7]		0.9	[0.3;2.6]	
	≥ median	9	88	2.1	[1.0;4.5]	0.14	1.6	[0.7;3.7]	0.51
Pesticides	Not exposed	77	1461		reference			reference	
	1 st tertile	7	144	1.0	[0.4;2.3]		0.9	[0.4;2.1]	
	2 nd tertile	10	138	1.2	[0.6;2.5]		1.2	[0.6;2.4]	
	3 rd tertile	10	154	0.8	[0.4;1.7]	0.88	0.8	[0.4;1.7]	0.92

^{*} ORs adjusted for age, country, alcohol drinking, body mass index and education[†] ORs adjusted for age, country, alcohol drinking, body mass index and exposures to other environmental estrogens listed in the table