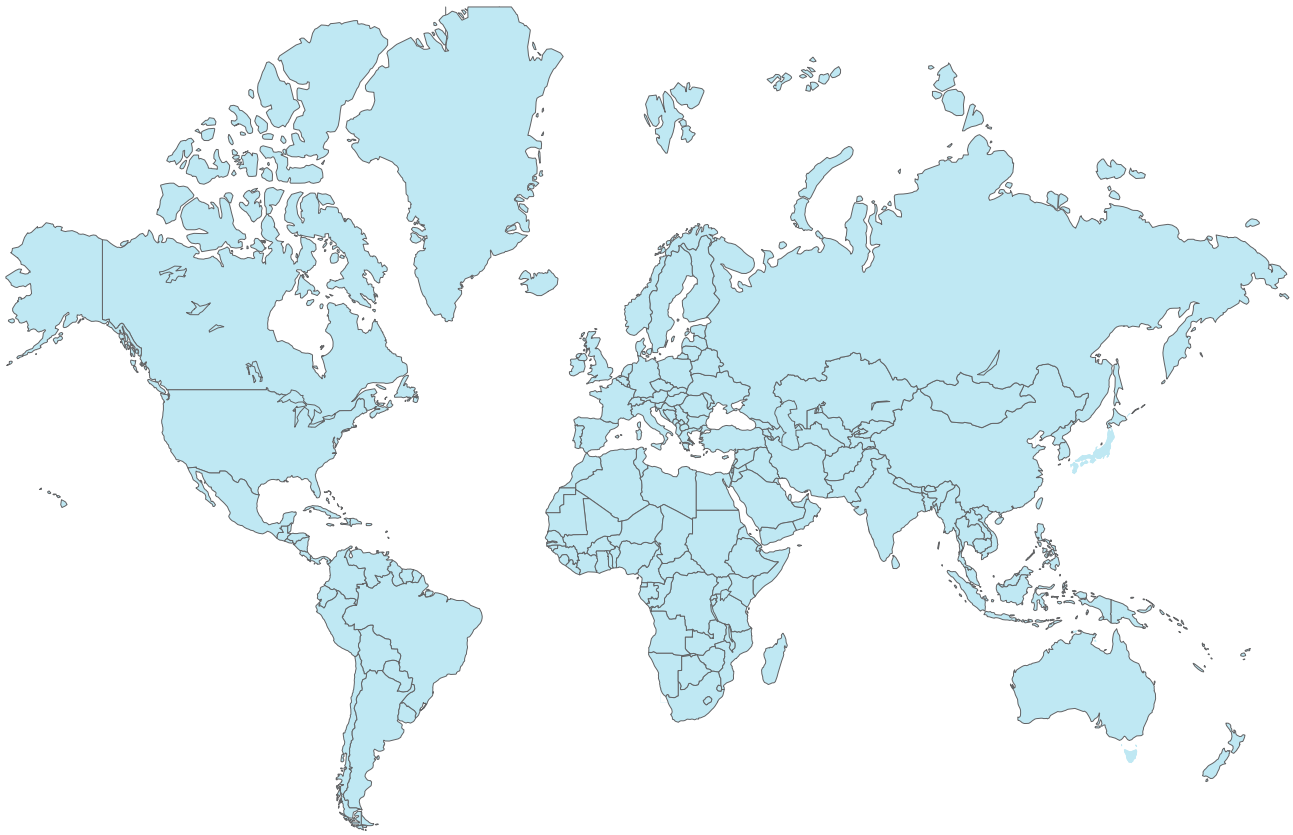
International Cancer
Research Partnership

Environmental Influences in Breast Cancer:

An analysis of the International Cancer Research Portfolio



A report from the International Cancer Research Partnership

ICRP Partners

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Canadian English spelling has been used throughout.

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Executive Summary

About the ICRP

The International Cancer Research Partnership's mission is to add value to cancer research efforts internationally by fostering collaboration and strategic co-ordination between cancer research organizations. The vision is that all funders of cancer research collaborate to enhance the impact of research on individuals affected by cancer.

The ICRP is an alliance of governmental and charitable organizations funding regional, national and international cancer research grants and awards. Members of the ICRP submit current and historical research funding information to a common database and share best practices to increase the efficiency of research administration and management. The ICRP database represents a significant portion of the cancer research performed in North America and Europe, and is estimated to cover a significant proportion of worldwide cancer research investment outside the industrial sector. Key information about ongoing and historical research funding is made available to the public[1] and to the research community. Detailed analysis at the level of individual award finances is made available to partner organizations.[2] Research funding organizations are invited to join this initiative.

Environmental influences on breast cancer

Breast cancer is the second most common cancer, and by far the most common cancer in women worldwide. The International Agency for Research on Cancer (IARC) reported that there were 1.67m new cases in 2012, and noted that while mortality rates have begun to decline in recent decades in some countries, incidence rates have continued to rise in most regions.[3] However, research has shown that only about 5-10% of breast cancer is attributable to genetic predisposition,[4] and only about one third of cases are attributable to known genetic or other risk factors. This report also notes that the synthetic chemicals in the environment have also increased significantly in recent decades, fuelling concern that environmental factors may be a significant contributor to the increase in breast cancer incidence.

Key findings

- There is some concern over general decline in numbers of awards and research funding in this area. Between 2006 and 2010, the numbers of active awards declined and funding levels also fell (Table 1).
- Most research is focussed on behavioural/ lifestyle factors in breast cancer, e.g., diet, alcohol intake, shift work patterns (see Figure 3).
- It is encouraging that multi-category research awards increased slightly, as a need for more research into multiple exposures has been highlighted.

Conclusions

The decline in numbers and research funding between 2006 and 2010 is concerning. As breast cancer incidence continues to increase, research efforts to understand the causes of increased incidence are essential. Further research investment in these areas may be required.

A number of ICRP partner organizations have invested significantly in new initiatives in this area (for example, Susan G. Komen announced a research initiative in 2013 focussed exclusively on environmental exposures,[5] and since 2004 the California Breast Cancer Research Program has dedicated a significant portion of its funding on research into environmental causes in breast cancer and disparities in breast cancer). This report provides a baseline from which organizations can monitor future research investment and activity.

1 *https://www.icrpartnership.org/database.cfm*
2 *https://www.icrpartnership.org/Partners/login.cfm*
3 *http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (Accessed 28/2/14)*
4 *http://www.niehs.nih.gov/health/assets/docs_a_e/environmental_factors_and_breast_cancer_risk_508.pdf*
5 *http://www.biomedcentral.com/1741-7015/12/99*
6 *http://cabreastcancer.org/sri/*

Purpose and scope of the analysis

In its summary of recommendations in 2013, the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)[8] noted that

> "...the complexity of breast cancer necessitates increased investment in research to explore compelling themes, such as mechanisms underlying breast cancer and breast density; epigenetic alterations — heritable changes that do not involve changes in DNA sequence — that occur over the life course; and gene-environment interactions..."

The IBCERCC also recommended that funding organizations plan strategically to accelerate the pace of scientific research on breast cancer and the environment.

This report aims to consolidate knowledge on activity and trends in research into environmental influences on breast cancer, and provide a baseline for future assessment of progress.

The working group looked at research into environmental influences in cancer, with the working definition proposed by the Institute of Medicine's 2011 report on breast cancer and the environment[9]

> "All influences not directly inherited through DNA"

The project scope was to assess the extent of research in the field, identify areas of highest activity, trends in activity and research gaps. Attempts have also been made to begin to understand the impact of funded research.

Brief overview of methodology

Research into environmental influences on cancer was expected to occur in specific Common Scientific Outline (CSO) areas.[10] A potential pool of 11983 breast cancer-relevant awards was narrowed to a manageable 1107 awards of relevance using a combination of keywords and CSO searches.

Each award was tagged with keywords relating to environmental influences derived from existing lists from expert sources (230 unique search terms, e.g., *benz* used to cover benzene, benzophenones, benzidine etc., see methodology appendix for further details); CSO category, Breast cancer percent relevance.[11] As expected, upon manual review, awards in CSO areas 1.2 and 6.2 without keywords (over 70% of awards) were of low, or no, relevance. The combination of CSO and keywords enabled the working group to isolate 1107 awards of specific relevance to the analysis.

Relevant awards were then coded with the assistance of keywords and manual review, to one or more of 6 specific categories of environmental research, or a general category if a specific research focus was not noted:

- Behavior-Lifestyle
- Behavior-Tobacco exposure
- Chemicals-Chemical pollutants
- Chemicals-Exogenous hormones
- Infection-Microorganisms
- Radiation
- General

For further details of the methodology used in this report, please refer to page 11).

8 https://www.niehs.nih.gov/about/assets/docs/summary_of_recs_508.pdf (Accessed 28/2/14)
9 Institute of Medicine's Breast cancer and the environment report (2011) http://www.iom.edu/Reports/2011/Breast-Cancer-and-the-Environment-A-Life-Course-Approach.aspx
10 CSO areas 2.1, 2.3, 1.2, 2.4 and 6.2
11 From a pool of 2377 awards extracted using the CSO as a primary filter. See the methodology section for further details.

Trends in investment

The general trend has been a decline in numbers of awards over the period from 2006 to 2010, a decline in investment between 2006 and 2008; and stabilisation of investment in 2010 (see **Table 1** and **Figure 1**). Over the whole period there has been a slight increase in average annual award value (from $0.26m to $0.30m, however the range is very wide: from under $1000 to over $11M).

On reviewing a subset of the awards, it was determined that a proportion were of low relevance to breast cancer (see **Figure 2**). As the ICRP database captures percentage relevance to breast cancer, the awards were assigned to relevance quartiles.

Awards with over 50% relevance to breast cancer were used for the remainder of the analyses (n=837), as these were considered to have a primary focus on breast cancer.

Table 1: Overall profile of the portfolio over three calendar years for the 1107 awards active either in 2006, 2008 or 2010.

	CY 2006	CY 2008	CY 2010
Numbers of awards	662	598	497
Research investment (USD)	$ 174.8 M	$ 146.0 M	$ 146.8 M

Figure 1: Overall profile of the portfolio in 2006, 2008 and 2010.

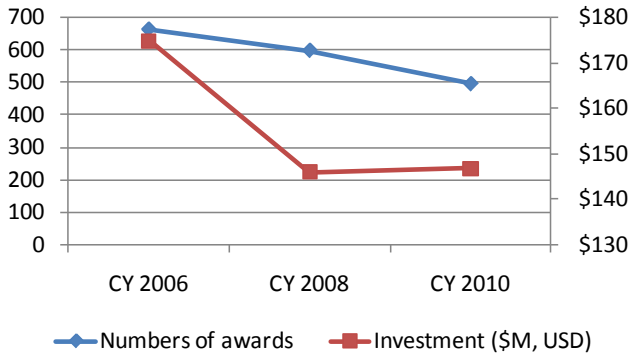
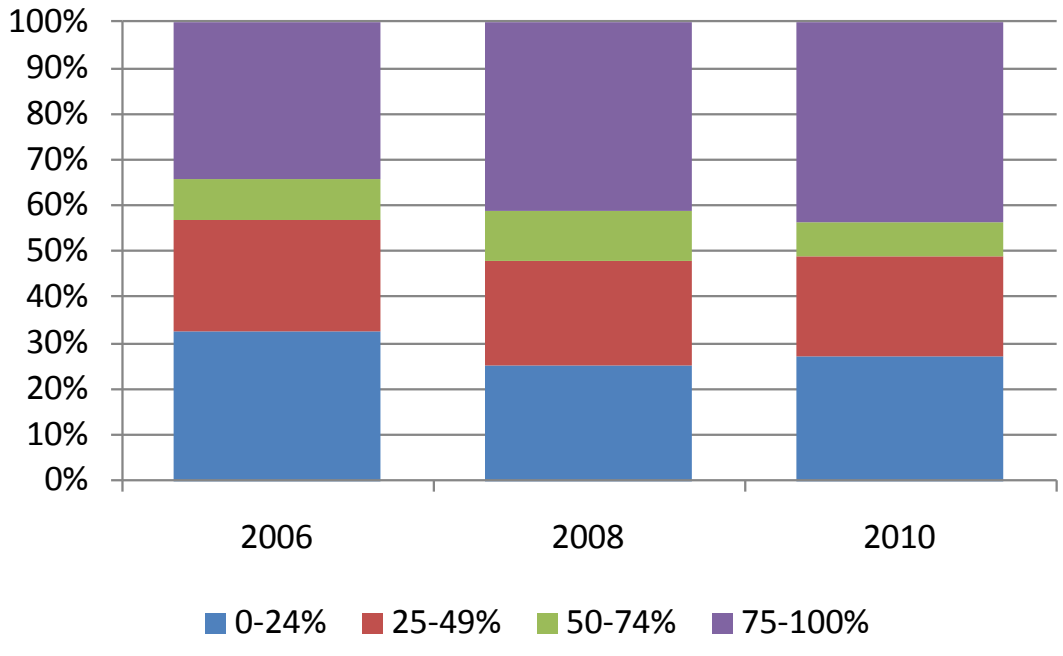


Figure 2: Breast cancer relevance percentage of awards.



Profile by Research Area

The profile of awards by research area is given below (**Figures 3.1** and **3.2**). Please note that individual awards may be classed to one or more research areas. No attempt was made to apportion these awards in this analysis.

The distribution by numbers of awards and spend are broadly similar. The strongest focus area is on lifestyle/environmental determinants of breast cancer (e.g., diet, alcohol intake, shift work patterns etc.) followed by the general category (wide-ranging studies focussing on all aspects of environmental causes, or where specific categories cannot be assigned). The higher focus on radiation exposure compared to tobacco exposure is, perhaps, surprising.

Figure 3.1: Distribution of awards across the environmental influences categories (# Numbers of awards)

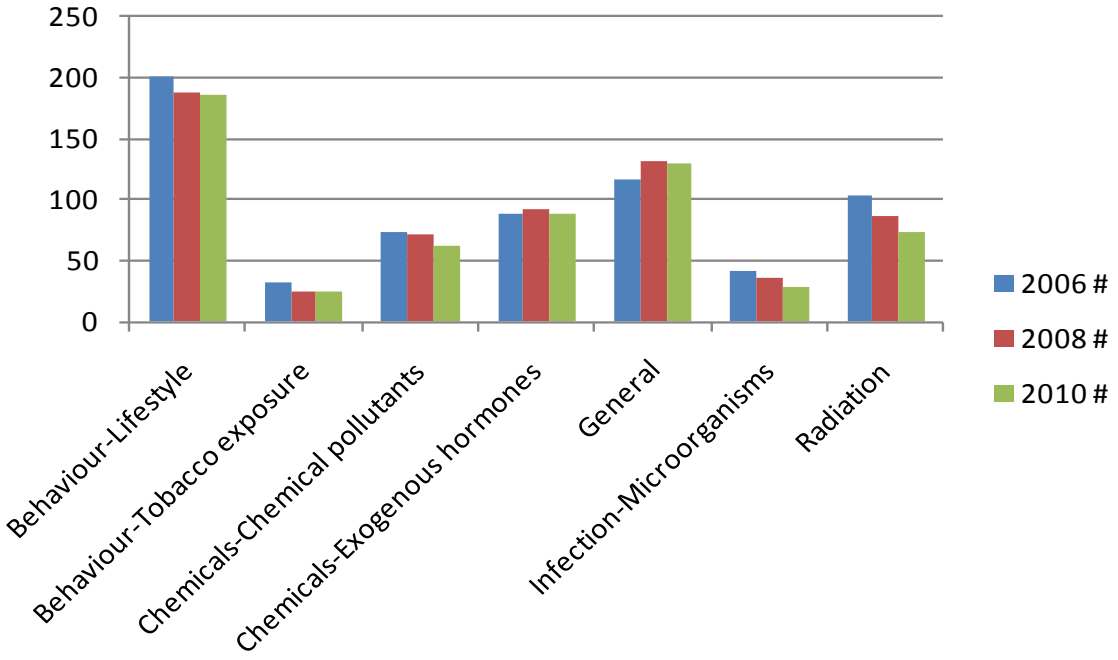
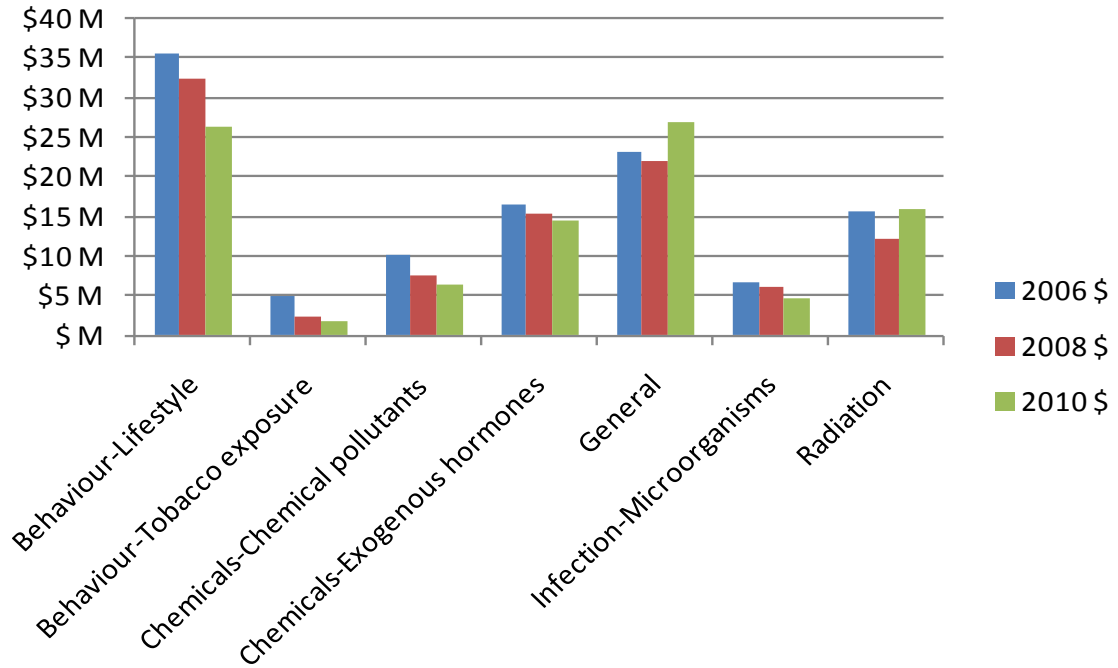


Figure 3.2: Distribution of awards across the environmental influences categories ($M, Research investment))

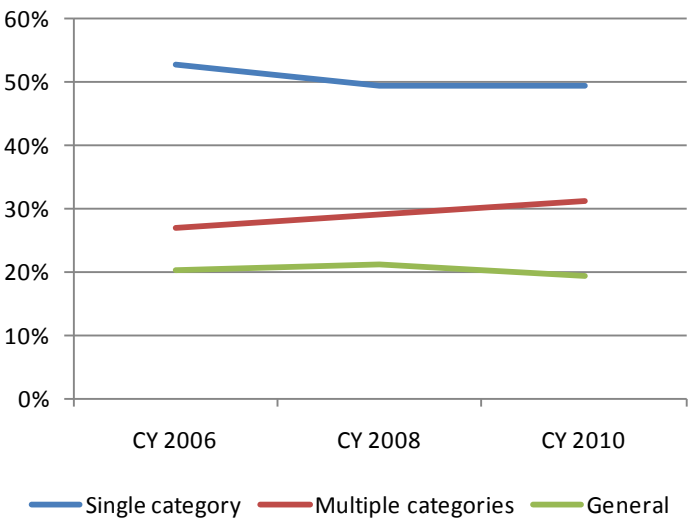


The President's Cancer Panel Report (citation) of 2008-09 highlighted the need for more research into multiple exposures. Analysis of the awards in the ICRP portfolio indicated that the majority were likely to have a focus on multiple categories, and that this multi-category research shows a small upward trend (see **Figure 4**, right). These awards may be more likely to consider multiple exposure factors than single category awards. It is notable that only 3 awards (3/1107) covered all 6 sub-categories.

Research in the "General" category may be more likely to address multiple factors, but it was not possible to be certain, based on the information in the abstracts.

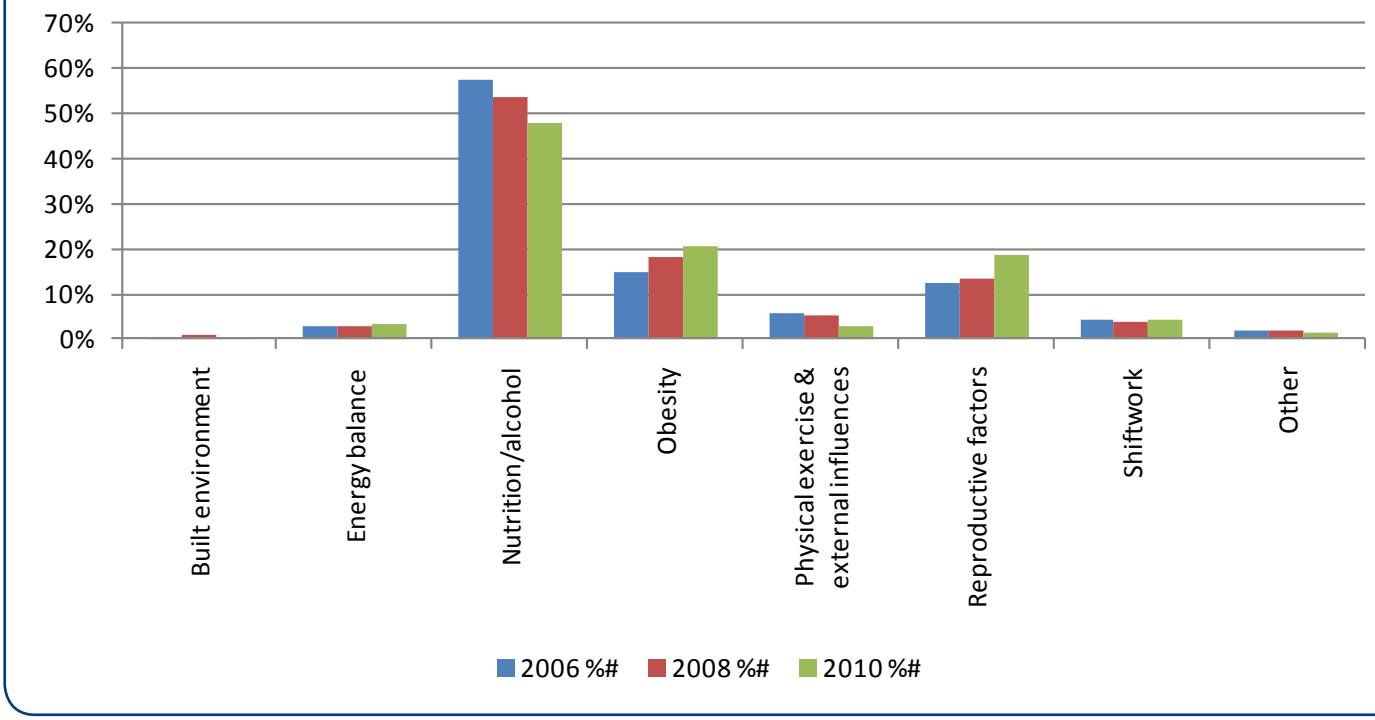
Further analysis of the Behavioural/Lifestyle category (**Figure 5**, below) reveals that the major area of activity is in the role of nutrition/alcohol in cancer, closely followed by the contribution of obesity and reproductive factors (age of menarche, parity etc.).

Figure 4: Numbers of awards showing research activity across multiple sub-categories



Year	Single category	Multiple categories	General
2006	53%	27%	20%
2008	50%	29%	21%
2010	50%	31%	19%

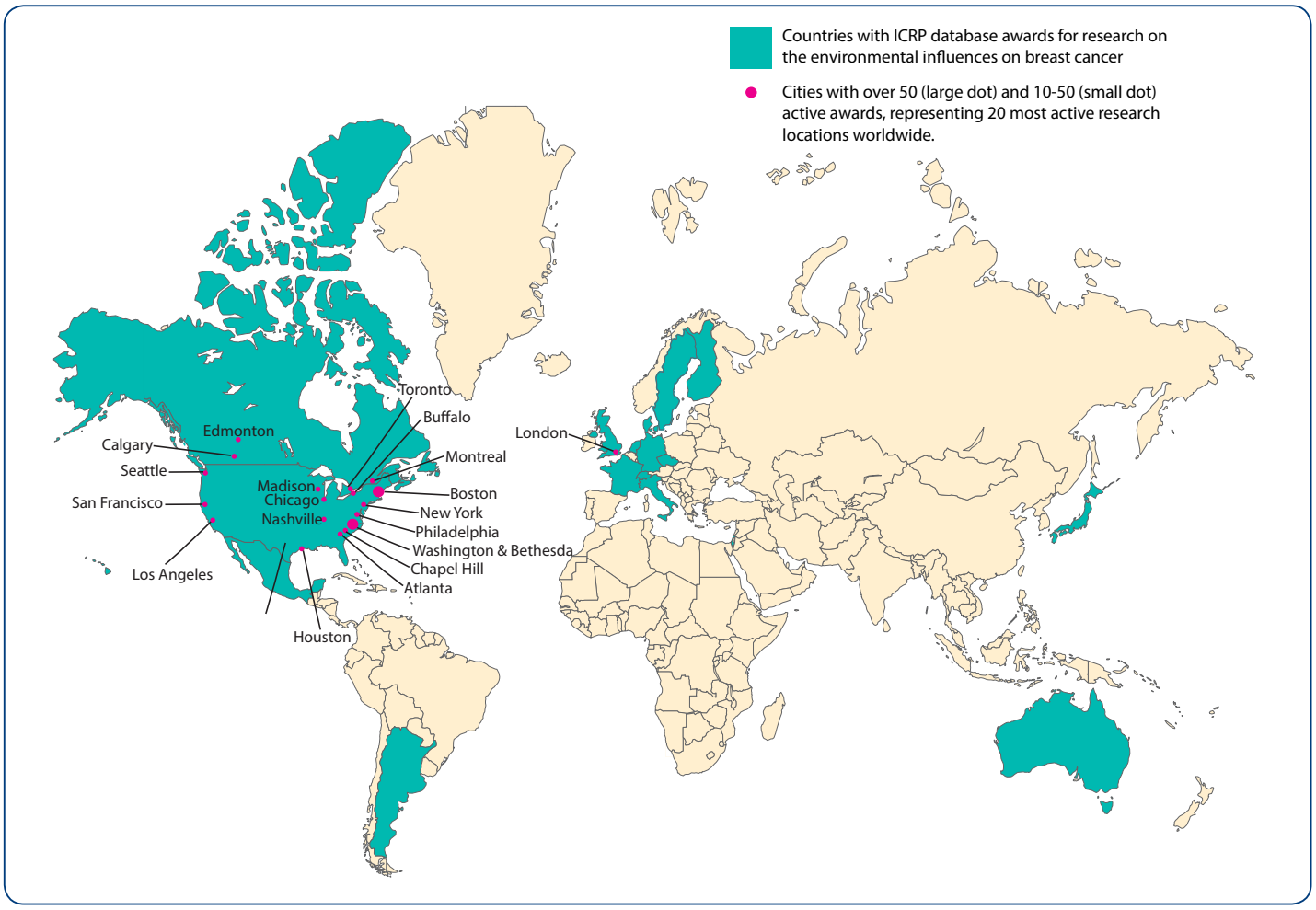
Figure 5: Breakdown of Behavioral-Lifestyle awards.



Research clusters

In assessing the status of a research field, it can be helpful for research funders to map out where this research is being conducted, to understand how existing and potential collaborations advance research.

Research in environmental influences of breast cancer research in the ICRP dataset is primarily conducted in the following locations:



The behavioral/lifestyle category was of particular interest to the group. The table below shows clusters of research activity in this field in research institutions.

It should be noted that this reflects only awards funded by ICRP partner organizations, and therefore the picture is not complete, especially for countries whose funding organizations are not included in the ICRP database.

Figure 6: Research institutions with the highest level of research activity in sub-categories.

Behaviour-Lifestyle			Behaviour-Tobacco exposure			Chemicals-Chemical pollutants		
City	Research Institution	%	City	Research Institution	%	City	Research Institution	%
Bethesda	National Cancer Institute	8%	Bethesda	National Cancer Institute	8%	Bethesda	National Cancer Institute	12%
Seattle	Fred Hutchison Cancer Research Center	3%	Oxford	University of Oxford	5%	Montréal	McGill University	4%
Boston	Brigham and Women's Hospital	3%	San Francisco	University of California	5%	Nashville	Vanderbilt University	3%
Washington	Georgetown University	2%	Atlanta	American Cancer Society	5%	Washington	Georgetown University	3%
Buffalo	Roswell Park Cancer Institute	2%	Nashville	Vanderbilt University	4%	Madison	University of Wisconsin	3%
Chemicals-Exogenous hormones			**Infection-Microorganisms**			**Radiation**		
City	Research Institution	%	City	Research Institution	%	City	Research Institution	%
Bethesda	National Cancer Institute	7%	Bethesda	National Cancer Institute	16%	Bethesda	National Cancer Institute	14%
Madison	University of Wisconsin	5%	Albuquerque	University of New Mexico	6%	Washington	Georgetown University	3%
Seattle	Fred Hutchison Cancer Research Center	5%	Chicago	The University of Chicago	6%	New York	NEW YORK UNIVERSITY	3%
Washington	Georgetown University	4%	Philadelphia	University of Pennsylvania	5%	Durham	DUKE UNIVERSITY	3%
Windsor	University of Windsor	3%	Boston	Tufts University	4%	Toronto	Cancer Care Ontario	3%

Research Funding

Research into the environmental influences on breast cancer in the ICRP database is funded by a wide range of organizations (see **Figure 7**, right) and the US National Institutes of Health is the predominant funder.

From analysis of publications, it is evident that the US NIH is the predominant producer of publications in the field. Non-ICRP funding organizations producing significant research in the field include the National Natural Science Foundation of China and the European Union.

Figure 7:

Country	Funding organizations	Total	% of portfolio
Australia	National Breast Cancer Foundation	9	0.8%
Canada	Canadian Cancer Research Alliance organizations	216	19.5%
France	Institut National du Cancer	2	0.2%
Netherlands	KWF Kankerbestrijding / Dutch Cancer Society	4	0.4%
UK	NCRI organizations	56	5.0%
US	American Cancer Society	30	2.7%
US	American Institute for Cancer Research	9	0.8%
US	Avon Foundation for Women	49	4.4%
US	California Breast Cancer Research Program	29	2.6%
US	National Institutes of Health	495	44.6%
US	Oncology Nursing Society Foundation	2	0.2%
US	Susan G. Komen for the Cure	59	5.3%
US	U. S. Department of Defense, CDMRP	149	13.4%

Search strategy

A combination of keywords and CSO codes were used to assess the relevance of ICRP awards to environmental influences. There was a wide range of keywords per project (0-15). Manual review of a selection of awards was used to test the assumption that a combination of keywords and CSO areas could be used to assess the relevance of the awards to environmental influences (Figure 8). The results of a coding pilot enabled the working group to focus manual coding efforts on a relatively small percentage of the overall portfolio (15%). It is anticipated that this combination of CSO and keyword analysis will facilitate analysis of the large volume of data contained in the ICRP database. As expected, the majority of awards coded to CSO2.1 or 2.3 were relevant to the analysis. The vast majority of those coded to the other CSO areas were not relevant (75% of those in CSO1.2, 2.4 or 6.2 had 0 (57%) or 1 (18%) keyword. Of those with 1 keyword, this was often ambiguous and not necessarily of relevance to environmental influences.). However keyword tagging did allow us to identify a small number of potentially relevant awards outside the expected CSO areas (i.e., those with multiple relevant keywords (1-2%)).

Figure 8: Search strategy

Awards coded to	Expected to be	True?
CSO 2.1/2.3 AND with >3 keywords	Very relevant	Yes, ALL included
CSO 2.1/2.3 AND with 1-3 keywords	Relevant	Yes, ALL included
CSO 2.1/2.3 AND with 0 keywords	Possibly relevant	42% included, rest excluded
CSO 1.2, 2.4 or 6.2 with 0 keywords	Irrelevant	Yes, ALL excluded
CSO 1.2, 2.4 or 6.2 with 1-3 keywords	Possibly relevant	59% excluded, rest included
CSO 1.2, 2.4 or 6.2 with >3 keywords	Possibly relevant	Yes, ALL included

Figure 9: Refinement of portfolio using search strategy

CSO category	Not relevant	Relevant	Total
CSO1.2, 2.4 (not 100%) or 6.2	1046 (44%)	184 (8%)	1230 (52%)
CSO2.1 or 2.3	196 (8%)	902 (38%)	1098 (46%)
CSO2.4 alone	28 (1%)	21 (1%)	49 (2%)
Grand Total	1270 (53%)	1107 (47%)*	2377 (100%)

Overall, 47% of the awards extracted with the CSO filter were found to be relevant by keyword analysis (Figure 9). As expected, the majority were in the CSO2.1 and 2.3 categories, a few in the linked etiology infrastructure category (CSO2.4) and a small number in the other CSO areas.

Keyword coding methodology

The 2377 awards extracted from the database using the CSO filter were 'tagged' with keywords using an excel program[12] (using over 300 individual keywords such as acrylamide or propylene) derived from the American Cancer Society (ACS) list of known and probable carcinogens,[13] IARC list of agents with sufficient or limited evidence of carcinogenicity,[14] IRIS database,[15] and the NIEHS 12th Report on Carcinogens,[16] grouped to the following areas:

- Behaviour-Lifestyle
- Behaviour-Tobacco exposure
- Chemicals-Chemical pollutants
- Chemicals-Exogenous hormones
- General
- Infection-Microorganisms
- Radiation

The keyword list was reviewed by colleagues at the California Breast Cancer Research Program (CBCRP) and keywords linked to chemotherapeutic drugs (etiology of secondary cancer) were removed for purpose of this analysis.

12 Developed by and used with the permission of Mr Andrew Knowles, Cancer Research UK
13 http://www.cancer.org/cancer/cancercauses/othercarcinogens/generalinformationaboutcarcinogens/known-and-probable-human-carcinogens (accessed 12 May 2014)
14 http://monographs.iarc.fr/ENG/Classification/Table4.pdf (accessed 12 May 2014)
15 http://www.epa.gov/iris/search_human.htm (accessed 12 May 2014)
16 http://ntp.niehs.nih.gov/?objectid=03C9AF75-E1BF-FF40-DBA9EC0928DF8B15 (accessed 12 May 2014)

Currency conversion

Average yearly interbank rates were used for conversion of other currencies to USD in 2006, 2008 and 2010. Inflation was not taken into account for the purpose of this analysis.

Breast cancer relevance

The ICRP database captures percentage relevance to cancer type routinely. Awards in this dataset were split into quartiles (0-24% relevance to breast cancer, 25-49%, 50-74%, 75-100%).

Data coverage

The ICRP database contains pooled portfolio data from over 80 organizations and institutes in the USA, Canada, Japan, UK, Australia, France and the Netherlands; and includes data from the world's largest funder of cancer research, the US National Institutes of Health. It is evident that this analysis is limited to data available in the system. Analysis of publication output in the field since 2006 has been used to estimate the extent of coverage of the ICRP database in this research area.

Analysis of publications from 2006 to 2013 (defined by the MeSH terms "environmental carcinogens" and "breast cancer") suggests that the ICRP organizations part or co-fund approximately 50% of all publications in this area .

The NCI/NIH accounted for the majority of publications (41%). The most significant non-ICRP funders were the European Union (4%) and the National Natural Science Foundation of China (3%).

Data caveats & notes

NCCJapan

The NCC Japan has recently started to upload portfolio data to ICRP. Only awards active in the CY 2010 are included in this analysis.

Acknowledgements

Working party:
Dr Senaida Poole (CBCRP), Dr Marc Hurlbert (Avon), Dr Kari Wojtanik (Komen), Dr Samantha Finstad (NCI), Dr Lynne Davies (ICRP). We are grateful to graduate student interns Allison Gonzalez and Connie Min at the California Breast Cancer Research Program for assistance with coding review.

Current members of the ICRP (May 2014)
Over 80 funding organizations and institutes

US

- American Cancer Society*
- American Institute for Cancer Research
- Avon Foundation Breast Cancer Crusade
- California Breast Cancer Research Program*
- Congressionally Directed Medical Research Programs, US Department of Defense*
- National Institutes of Health (including the National Cancer Institute)*
- National Pancreas Foundation
- Oncology Nursing Society Foundation*
- Pancreatic Cancer Action Network
- Susan G. Komen®*

Australia

- Cancer Australia**
- National Breast Cancer Foundation

Canada

- Canadian Cancer Research Alliance *(currently representing 19 funding organizations/programs)*

France

- Institut National du Cancer (French National Cancer Institute) & research co-funded with Direction Générale de l'Offre des Soins (Ministry of Health)

Japan

- National Cancer Center

Netherlands

- KWF Kankerbestrijding (Dutch Cancer Society)

UK

- National Cancer Research Institute* *(representing 20 funding organizations)*

Note: the founding partner organizations are marked with an asterisk (*) above.

** Cancer Australia joined ICRP in 2014, its data is in preparation for inclusion in the ICRP database and is not included in the current report

Appendix A
Description of the CSO

The Common Scientific Outline or 'CSO' is a classification system organized into seven broad areas of scientific interest in cancer research and further divided into sub-categories:

CSO area:	1 - Biology	2 - Etiology	3 - Prevention	4 - Early detection, diagnosis and prognosis	5 - Treatment	6 - Cancer control, survivorship and outcomes	7 - Scientific model systems
1	Normal functioning	Exogenous Factors in the Origin and Cause of Cancer	Interventions to Prevent Cancer: Personal Behaviors That Affect Cancer Risk	Technology Development and/or Marker Discovery	Localized Therapies – Discovery and Development	Patient Care and Survivorship Issues	Development and Characterization of Model Systems
2	Cancer Initiation: Alterations in Chromosomes	Endogenous Factors in the Origin and Cause of Cancer	Nutritional Science in Cancer Prevention	Technology and/or Marker Evaluation With Respect to Fundamental Parameters of Method	Localized Therapies: Clinical Applications	Surveillance	Application of Model Systems
3	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	Chemoprevention	Technology and/or Marker Testing in a Clinical Setting	Systemic Therapies: Discovery and Development	Behavior	Resources and Infrastructure Related to Scientific Model Systems
4	Cancer Progression and Metastasis	Resources and Infrastructure Related to Etiology	Vaccines	Resources and Infrastructure Related to Detection, Diagnosis, or Prognosis	Systemic Therapies: Clinical Applications	Cost Analyses and Health Care Delivery	--
5	Resources and Infrastructure Related to Biology	--	Complementary and Alternative Prevention Approaches	--	Combinations of Localized and Systemic Therapies	Education and Communication	--
6	--	--	Resources and Infrastructure Related to Prevention	--	Complementary and Alternative Treatment Approaches	End-of-Life Care	--
7	--	--	--	--	Resources and Infrastructure Related to Treatment and the Prevention of Recurrence	Ethics and Confidentiality in Cancer Research	--
8	--	--	--	--	--	Complementary and Alternative Approaches for Supportive Care of Patients and Survivors	--
9	--	--	--	--	--	Resources and Infrastructure Related to Cancer Control, Survivorship, and Outcomes Research	-

Subcategory

The CSO is complemented by a standard cancer type coding scheme. Full details of the system can be found at https://www.icrpartnership.org/CSO.cfm.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