Occupational exposures and postmenopausal breast cancer: impact of sensitivity analysis

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The Montreal Study - 1

- 556 incident cases of breast cancer (ICD-9 174), histologically confirmed, 50-75 years old. Greater metropolitan area of Montreal, 1996-97
- 613 incident cancer controls (32 selected sites)
  - Frequency-matched (age, date of Dx, hospital)
  - Excluding : lung, bronchus & trachea, brain & CNS, pancreas, liver & intrahepatic bile ducts, leukemia & lymphomas, non-melanoma skin cancer
- Telephone & face-to-face interviews
  - Socio-demographic information
  - Complete job histories + task description (specific questionnaires)

The Montreal Study - 2

- ***Translation*** of jobs into occupational exposures by team of hygienists
  - Intensity of exposure (low, medium, high)
  - No. hours exposed in regular work day
  - % days exposed
  - Confidence of coder that job was ever exposed
- ***Specific recodes***
  - Solvents with reactive metabolites : 14 solvents

    E.g.: benzene, carbon tetrachloride, chlorobenzene, methylene chloride, tetrachloroethylene, trichloroethylene, styrene, xylenes, etc.

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3

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Selected Findings - 1

Exposure Prevalence

Substance Name	*Cases (n=556)*		*Controls (n=613)*	
	N	*%*	N	*%*
Electromagnetic fields	437	*78.6*	450	*75.0*
Volatile organic liquids	228	*41.0*	223	*36.4*
Synthetic fibres	103	*18.5*	112	*18.3*
Org. solvents / reactive metabolites	62	*11.1*	53	*8.6*
Nylon fibres	58	*10.4*	54	*8.8*
PAHs from petroleum	41	*7.4*	31	*5.1*
Monocyclic aromatic hydrocarbons (MAHs)	33	*6.0*	31	*5.1*
Rayon fibres	29	*5.2*	31	*5.1*
Acrylic fibres	26	*4.7*	18	*2.9*

4

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Selected Findings - 2

(per 10-year increase of any exposure)	*All ages*		*≤ age 35 years*	
	OR	***95% CI***	***OR***	***95% CI***
Acrylic fibres	1.93	*1.16-3.23*	7.69	*1.47-40.2*
Electromagnetic fields	1.13	*0.94-1.35*	1.40	*0.98-2.02*
Monocyclic Arom. Hc (MAHs) [E+/P-]	3.24	*1.23-8.53*	4.63	*0.89-24.02*
Nylon fibres	1.14	*0.87-1.50*	1.99	*1.02-3.88*
Org. solvents / reactive metabolites [E+/P-]	1.73	*0.88-3.39*	3.31	*1.07-10.20*
PAH's from petroleum	1.52	*0.97-2.39*	2.38	*1.00-5.67*
Rayon fibres	1.51	*1.00-2.28*	2.65	*0.91-7.73*

5

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Labrèche *et al*., *Occup Environ Med* 2010; 67:263-9.
Labrèche *et al*., *Am J Ind Med* 2003; 44:643-52.

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Q - Mechanistic Issues

1. Substances hypothesized to behave as xenoestrogens
   ∴ mimic estrogens
   → should be associated to ↑ in hormonal cancers (breast, but also ovary, uterus)

➢ In our study, controls: other cancer sites,
∴ risks obtained with all cancer controls *vs.* risks obtained after excluding hormonal cancers from control series
→ risks should ↑ if hormonally-mediated pathway

2. Substances hypothesized to act through another mechanism (e.g. organic solvents with reactive metabolites)
   → risks should not change

6

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Findings - Mechanistic Issues

	OR, All ages		*OR, ≤ age 35 years*	
	All controls	***Excl. hormonal cancers***	**All controls**	***Excl. hormonal cancers***
Acrylic fibres	1.93	*1.79*	7.69	*9.11*
Monocyclic Arom. Hc (MAHs) [E+/P-]	3.24	*4.48*	4.63	*5.94*
Nylon fibres	1.14	*1.13*	1.99	*1.90*
Org. solvents / reactive metabolites [E+/P-]	1.73	*1.71*	3.31	*3.40*
PAH's from petroleum	1.52	*1.40*	2.38	*2.26*
Synthetic fibres	1.07	*1.08*	1.53	*1.72*

7

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∴ Data consistent with xenoestrogenic mechanism for MAHs & for early exposures to acrylic fibres, but not for organic solvents…

Q - Fibres or Co-Exposures?

- Strong effect observed for acrylic fibres, but small numbers…
- Jobs & industries contributing to largest # of years of exposure:
  - Sewing-machine operator, Machine presser (garment & fabric, cleaning & pressing), Garment inspector
  - Dress / pants / other clothing & apparel industries, Clothing contractors
- Co-exposures common in textile industries:
  - Volatile organic liquids, EMFs, lubricating oil, etc.
  - High correlations between fibres: acrylic-rayon, acrylic-silk
  - Lower or inexistent correlations (< 0,2) between fibres & EMFs, organic solvents

8

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Findings 1 – Fibres or Co-Exposures?

- Correlations between years of exposures to acrylic fibers and years of exposure to other agents
  - different between cases & referents

9

	Nylon fibres	Polyester fibres	Rayon fibres	Wool fibres	EMFs	Solvents
Cases	0.46	0.58	0.71	0.62	0.20	0.03
Referents	0.41	0.38	0.54	0.26	0.12	0.00

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Findings 2 - Fibres or Co-Exposures?

	OR, All ages		*OR, ≤ age 35 years*	
	OR	*95% CI*	*OR*	*95% CI*
Acrylic fibres	1.93	*1.16-3.23*	7.69	*1.47-40.2*
Acrylic fibres, adj. for nylon fibres	1.96	*1.12-3.43*	8.12	*1.41-46.7*
Acrylic fibres, adj. for nylon fibres ≤ age 35 years	1.74	*1.02-2.98*	5.99	*1.06-33.9*
Acrylic fibres, adj. for polyester fibres	2.24	*1.26-4.00*	11.56	*1.93-69.3*
Acrylic fibres, adj. for polyester fibres ≤ age 35 years	1.83	*1.06-3.16*	7.52	*1.25-45.1*
Acrylic fibres, adj. for rayon fibres	1.76	*0.95-3.28*	6.06	*1.06-34.8*
Acrylic fibres, adj. for rayon fibres ≤ age 35 years	1.77	*1.01-3.11*	6.66	*1.06-34.8*
Acrylic fibres, adj. for EMFs	1.86	*1.11-3.13*	7.16	*1.36-37.6*
Acrylic fibres, adj. for EMFs ≤ age 35 years	1.89	*1.12-3.17*	7.25	*1.37-38.4*

10

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∴ Little impact of adjustment for other fibres or EMFs on risk associated with acrylic fibres, but…

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Q - Exposure-response gradient?

- Does risk increase with cumulative exposure/duration of exposure?
- Example with acrylic fibres

11

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Findings - Exposure-response gradient?

Example: acrylic fibres	*All ages*			*≤ age 35 years*		
	n	***OR***	***95% CI***	***n***	***OR***	***95% CI***
Substantial (≥ 5 years, moderate & high exposures)	0	-	-	0	-	-
Non-substantial (≥ 5 years, low, moderate & high exposures)	15	4.01	*1.32 - 12.20*	11	7.52	*1.43 - 39.58*
Other exposures (some, < 5 years)	11	1.29	0.46 - 3.61	15	1.29	0.55 - 3.03
1st tertile*	10	1.35	*0.45-4.00*	8	2.67	*0.57-12.41*
2nd tertile*	7	1.81	*0.52-6.35*	6	10.86	*1.52-77.39*
3rd tertile*	9	5.11	*1.12-23.23*	4	6.52	*0.74-57.54*
Cumulative, per 10-year increase	26	1.55	*0.99-2.44*	18	7.69	*1.47-40.24*

* 1st tert.: ≤ 3.5 years
* 2nd tert.: > 3.5 y. & ≤ 19.5 y.
* 3rd tert.: > 19.5 y.

1st tert.: ≤ 2.5 years
2nd tert.: > 2.5 y. & ≤ 9.5 y.
3rd tert.: > 9.5 y.

∴ Suggestive results, but small numbers!!

12

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In Summary -1

- Data with strengths & limitations
  - Good response rates, population-based study; most accepted risk factors for breast cancer show increased risk; use of a more accurate system for assigning exposures than job titles, self reported exposures or JEMs
  - Indirect retrospective estimations of exposure (↘ risk estimates); cancer controls (if their cancer associated with exposures under scrutiny, ↘ risk estimates)
  - Possible subgroups with different risks (varying hormonal receptor status, time windows of exposure…)
  - Small numbers for specific exposures

13

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In Summary - 2

- Sensitivity analyses: answers to some questions…
  - Mechanisms:
    - Data consistent with xenoestrogenic mechanism for MAHs & for early exposures to acrylic fibers; & with different mechanism for organic solvent exposure
  - Effect from exposure or co-exposures?
    - Some effects appear attributable to acrylic fibres, but effect of high correlations with co-exposures still possible
  - Dose-response relationships?
    - Suggested, but small numbers!!

14

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Remaining Questions…

- Caveats:
  - Low prevalence for specific exposures
  - Study designed to look at organic solvents & EMFs
  - First reports for some agents : leads for further research (e.g. acrylic fibers)
- Impact of sensitivity analyses
  - No important change in conclusions → reassurance on results robustness ?
- Equilibrium between data dredging &sensitivity analysis?
  - Is it worth while, especially for "incidental" findings?
  - Does it convince you?

15

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