REVIEW

Occupational risk factors for female breast cancer: a review

Mark S Goldberg, France Labrèche

Abstract

Objectives—Although progress has been made in identifying personal risk factors and in improving treatment for female breast cancer, incidence rates continue to increase. With women now occupying a sizable fraction of the workforce, it is worth inquiring whether there are occupational risk factors for breast cancer. This is a review of occupational studies on female breast cancer.

Methods—Suitable reports and published articles with associations of female breast cancer and occupation were identified from technical reports, by searching the MEDLINE bibliographic data base, and by reviewing each paper on cancer that was published in 20 major journals during the period from about 1971-94.

Results—A total of 115 studies were identified; 19 studies relied exclusively on data collected for administrative purposes, and there were four incident case-control studies and 92 cohort studies. Although data for individual industries, occupations, and exposures were sparse, there was limited evidence of an association with employment in the pharmaceutical industry and among cosmetologists and beauticians. Associations were also found for chemists and occupations with possible exposure to extremely low frequency electromagnetic fields, but potential methodological weaknesses preclude drawing any definite conclusions. There was little support for increased risks among textiles workers, dry cleaning workers, and nuclear industry workers.

Conclusions—Few high quality occupational studies directed specifically toward women have been carried out to allow the unambiguous identification of occupational risk factors for breast cancer. It is suggested that investigations that account for non-occupational risk factors and that assess exposure in a more detailed way be carried out. One strategy already suggested is to conduct population based, case-control studies in which subjects are interviewed about their occupational histories and exposure to chemical and physical agents which are then attributed from the job descriptions by a team of experts. These studies can then be supplemented when necessary with cohort studies of specific populations.

Keywords: cancer female breast; occupational exposure; epidemiology; literature review

Breast cancer in western societies affects almost one in 10 women during their lifetime¹ and is the leading cause of death from cancer in women.² Over the past quarter century, the focus of research has been to improve treatments and to identify personal risk factors, such as family history of cancer and reproductive factors.³ Observations on reproductive factors have led to the hypothesis that breast cancer is caused by early and extended exposures to hormonal oestrogen and progesterone.⁴ Environmental risk factors have also been studied, but not as extensively. Exposure to ionising radiation has been shown to be clearly associated with a risk of breast cancer.⁵ Other environmental exposures have been investigated recently, including consumption of alcohol,⁶ exposure to persistent organochlorine compounds,⁷ and dietary fat,⁸ although results are controversial.⁹⁻¹⁰

Against this large research effort is the unfortunate fact that incidence rates in most western societies have continued to increase over the past few decades.^{2,11-13} The reasons for these increases are largely unknown, but could be related to early detection in mass screening programmes,¹⁴ to temporal changes in accepted and suspected risk factors, to changes in the pathological definition of breast cancer, or to an artifact of detecting "histologically malignant but biologically benign" tumours¹⁵ (although this seems doubtful¹³), or to other unidentified risk factors. It is likely that the accepted risk factors cannot account for a large fraction of cases or for all of the growth in incidence rates.¹⁶

As women have taken a more active role in the workforce since the 1960s,¹⁷ it is possible that the secular increases in incidence rates may be related in part to exposure to carcinogens in the workplace. Although the occupational setting has not been studied with the intensity given to personal risk factors, interest in this field has increased.¹⁸ In considering new avenues of research, it is timely to provide a review of the current state of knowledge of the occupational environment. We therefore present a summary of results for breast cancer from occupational studies conducted within the past 25 years.

Materials

Reports and published articles with the potential for investigating associations of female

Occupational and Environmental Health Unit, Public Health Department, Maisonneuve-Rosemont Hospital, Montréal, Québec and Department of Occupational Health, McGill University, Montréal, Québec
M S Goldberg
F Labrèche

Correspondence to:
Dr Mark Goldberg,
Occupational and Environmental Health Unit,
Public Health Department,
Maisonneuve-Rosemont
Hospital, 75 de Port-Royal
E, Suite 240, Montréal,
Québec, Canada H3L 3T1.

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Table 1 Journals and time periods covered by this review

Journal	Calendar period
American Industrial Hygiene Association Journal	1987-94
American Journal of Epidemiology	1965-94*
American Journal of Industrial Medicine	1971-94*
Annals of Epidemiology	1991-mid-1994
Annals of Occupational Hygiene	1987-92
Applied Occupational and Environmental Hygiene	1988-mid-1994
Archives of Environmental Health	1965-94*
British Journal of Cancer, with Supplements	1980-mid-1994
British Journal of Industrial Medicine	1965-94*
Cancer	1985-94
Cancer Causes and Control	1990-94
Cancer Research	1985-mid-1994
Epidemiology	1990-94
International Archives of Occupational and Environmental Health	1975-93
International Journal of Cancer, with Supplements	1985-93
International Journal of Epidemiology	1971-mid-1994*
Journal of Occupational Medicine	1965-mid-1994*
Journal of the National Cancer Institute	1971-mid-1994*
Journal of Toxicology and Environmental Health	1987-mid-1994
Scandinavian Journal of Work Environment and Health	1971-mid-1993*

*Review for 1971-90 carried out by Hoar Zahm *et al.*^{19,20}

breast cancer and occupation were identified by searching the MEDLINE bibliographic data base, and by reviewing each paper on cancer that was published in 20 major journals during the period from about 1971 to about mid-1994 (table 1). We benefited from the earlier review carried out by Hoar Zahm and colleagues^{19,20} of papers in eight journals published between 1971 and 1990. Excluded from consideration were studies of the radium dial painters because they have limited relevance to women's occupations after the second world war.

A total of 147 reports from 115 independent studies, including non-peer reviewed technical reports,^{29,33,44,45,61} were reviewed (table 2). Studies were classified by type of

Table 2 Distribution of the types of studies included in this review

Type of study (abbreviation)	Reports* n	References**
Studies based on administrative data:		
Mortality studies:		
Standardised mortality ratio (SMR)	4	21-24
Proportional mortality (PMR)	15	25-40
Mortality odds ratio (MOR)	3	41-43
Combination SMR/PMR	3	44, 45
Combination PMR/MOR	1	46
Combination SMR/MOR	1	47
Incidence studies:		
Proportional incidence ratio (PIR)	3	48-50
Standardised incidence ratio (SIR)	8	51-58
Combination SIR/PIR	1	59
Mortality/incidence studies:		
SIR/MOR	1	60
Number of reports	40	
Number of independent studies	19	
Case-control and cohort studies:		
Case-control (C-C), incidence	4	61-64
Cohort:		
SMR	56	
PMR/MOR	12	
Nested C-C (mortality)	1	
SIR	12	
SIR/SMR	10	
PH (incidence)	1	
Number of reports	106	See Table 3
Number of independent studies	92	
Total number of reports	147	
Total number of independent studies	115	

*The following studies were considered to be based on the same data base: five PMR studies from British Columbia^{30,32-35}; four studies from the United Kingdom^{21,40,44,45}; three studies from the Swedish cancer registry^{51,52,58}; four incidence studies from the Danish cancer registry^{48,53,54,56}; and 10 studies based on mortality data from the United States National Centre for Health Statistics (from about 25 American states).^{26,27,37-39,41-43,46,50}

**The studies by Aronson and Howe,²⁴ Seniori Costantini *et al.*⁴⁷ and the Danish^{48,53-54,56} and Finnish⁵⁵ studies, based on linking occupational data obtained at one point in time—for example, from census data—with subsequent cancer incidence or mortality data, were not considered as cohort studies in this report.

PH = proportional hazards analysis.

design, although some investigations did not fit neatly into one simple category. Nineteen studies (of 40 reports) relied on routinely collected data or data collected for other administrative purposes—for example, special labour force surveys²⁴—whereby mortality or cancer incidence statistics were calculated with or without census denominators—for example, proportional mortality (PMR) studies and standardised incidence ratio (SIR) studies, respectively. Twelve of these studies were based on mortality figures,²¹⁻⁴⁷ six studies were based on incidence data,⁴⁸⁻⁵⁹ and one study combined incidence and mortality.⁶⁰ There were also four incident case-control studies,⁶¹⁻⁶⁴ and 92 investigations of cohorts (from 106 reports; table 3).⁶⁵⁻¹⁷⁰

Results

The studies with routinely collected data usually covered a wide variety of occupational circumstances and were from different parts of the world.^{21-25,29,30,32-35,39,40,44-50,53,57} Other administrative studies, not all independent from these, were directed toward specific types of industries or occupations: agriculture,^{31,38,58,60} beauticians and cosmetologists,⁵⁹ electrical workers,^{42,43,56} electronics industry,⁵¹ health care workers,^{27,55} jewellers,³⁷ laundry and dry cleaning,^{26,41,54} pharmaceuticals,²¹ printing,⁵² shoe manufacturing,³⁶ telephone workers,⁴³ and textiles.²⁸

Two of the four case-control studies were population based,^{61,62} one was based on patients admitted to Roswell Park Memorial Institute, Buffalo, NY,⁶³ and the fourth⁶⁴ was a nested study among patients referred to a breast cancer screening clinic in New York City. In general, response rates in three of these studies were adequate⁶²⁻⁶⁴ and control populations were selected appropriately. The focus of the report by Franceschi *et al.*⁶² was on farming and agricultural occupations and that of Koenig and collaborators⁶⁴ was on cosmetologists. We assumed that in all of these studies there was the opportunity to investigate a wide variety of occupational circumstances.

Thirty three different occupations or industries were investigated in the cohort studies, as well as 16 different exposures to chemical agents (table 3). Eight occupational circumstances were studied more than twice: asbestos workers (eight independent studies); chemical and related workers (five studies); cosmetologists (four studies); pharmaceuticals (three studies); rubber industry (six studies); shoe manufacturing (four studies); textiles and garment workers (five studies); and x ray technicians and radiation workers (six studies).

Excluding cohort studies that relied on PMR or mortality odds ratio (MOR) analyses, the median number of women included in these studies was about 1500: 18 studies included more than 5000 subjects, and six studies included more than 10 000 subjects.^{73,77,80,96,134,135,153,154} The median number of breast cancer cases was 19 (mean of 64), and only five studies had more than 100 cases.^{75,76,80,134,135,153} Although table 3 shows that

Table 3 Design characteristics, occupational circumstances, and chemical exposures that were investigated in the cohort studies

	Reports n	Study design	Exposure- response*	Women n	Cases n	Relative risk† 95% CI	Statistical power(%)‡	Reference
Occupations or industries:								
Abattoirs	2	SMR	N	3935	26	0.7 (0.5-0.9)	100	65,66
Actors	1	PMR	N	NA	53	1.2 (0.9-1.5)	100	67
Aircraft maintenance	1	SMR	C	3138	30	0.7 (0.5-1.0)	100	68
Aircraft manufacturing	1	SMR	N	950	NR	NR (NC)	NC	69
Artists	1	PMR	N	NA	21	1.9 (1.2-2.9)	87	70
Cable manufacturing (chlorinated naphthalenes)	1	SMR	L	3042	47	1.0 (0.7-1.3)	100	71
Chemical industry, chemists	6	MOR	N	NA	30	1.6 (1.1-2.9)	97	72
		SMR	Y	10839	54	1.1 (0.8-1.5)	100	73
		MOR	N	NA	7	5.3 (2.8-10.1)	25	74
		SIR	S	NR	395	1.2 (1.0-1.3)	100	75,76
		SMR	S	NR	156	0.9 (0.8-1.0)	100	75,76
		SMR	S	24461	39	1.0 (0.7-1.4)	100	77
Cosmetologists	4	SMR	N	7736	5	0.6 (0.2-1.4)	78	78
		SMR	N	677	9	0.7 (0.3-1.3)	91	79
		SIR	N	677	7	0.6 (0.2-1.2)	90	79
		SIR	Y	11845	204	1.0 (0.9-1.2)	100	80
		SIR	N	3637	70	1.2 (1.0-1.6)	100	81
Dry cleaning	4	SMR	N	1109	19	1.0 (0.6-1.7)	97	82,83
		SMR	E	4046	36	1.0 (0.7-1.4)	100	84,85
Electric light manufacturing	1	SIR	N	1044	21	1.2 (0.8-1.8)	50	86
Foundry workers	2	SMR	Y	627	NR	NR (NC)	NC	87
		SMR	Y,L	2243	2	0.5 (0.1-1.9)	49	88
Furniture manufacture	1	SMR	N	6680	53	0.7 (0.5-0.9)	100	89
Gardeners	2	SMR	N	151	NR	NR (NC)	NC	90
		SIR	N	859	10	1.1 (0.5-2.1)	81	91
Jewellery workers	1	PMR	N	1083	NR	NR (NC)	NC	92
		PMR	N	NA	30	0.8 (0.5-1.1)	100	92
Laboratory workers	1	SMR	N	685	8	2.9 (1.2-5.7)	40	93
Leather tanning	1	SMR	Y,L	482	NR	NR (NC)	NC	94
		SIR	Y,L	482	19	1.5 (0.9-2.3)	91	94
Motor vehicle manufacturing	2	PMR	N	NA	5	1.1 (0.4-2.5)	56	95
		SMR	N	11271	52	0.7 (0.5-1.0)	100	96
Municipal workers	1	SMR	N	1199	10	0.8 (0.4-1.6)	89	97
Pathologists	1	SMR	N	803	4	1.6 (0.4-4.1)	37	98
Petroleum manufacturing workers	1	SMR	L	8249	20	1.0 (0.6-1.5)	98	99
Pharmaceuticals, pharmacy technicians	3	PMR	N	NA	22	1.8 (1.1-2.7)	90	100
		SIR	N	8499	70	1.1 (0.8-1.4)	100	101
		SIR	L,Y	5554	97	1.5 (1.2-1.8)	100	102
Polyurethane foam manufacture	1	SMR	Y	2465	11	0.7 (0.3-1.2)	95	103
		SIR	Y	2465	23	1.0 (0.6-1.4)	99	103
Pottery industry	1	PMR	N	946	NR	NR (NC)	NC	104
Pulp and paper, sawmills	2	SIR	L	849	8	0.6 (0.3-1.3)	90	105
		SIR	N	502	8	0.8 (0.4-1.7)	82	106
Reindeer breeders	1	SIR	N	757	5	0.4 (0.1-0.8)	92	107
Rubber and affiliated industry	7	SMR	N	4200	56	0.8 (0.6-1.1)	100	108,109
		SMR	N	3377	22	0.9 (0.6-1.4)	100	108,109
		SMR	N	1649	5	0.4 (0.1-1.0)	90	110
		SMR,SIR	L	4280	NR	NR (NC)	NC	111
		SMR	N	667	NR	NR (NC)	NC	112
		SMR	N	2492	6	0.6 (0.2-1.2)	85	113
		SIR	N	2492	11	0.6 (0.3-1.0)	100	113
		SMR	N	250	NR	NR (NC)	NC	114
Semiconductor workers	2	SMR	N	1526	7	0.5 (0.2-1.1)	91	115,116
		SIR	N	1526	20	0.8 (0.5-1.1)	100	115,116
Shoe manufacturing	4	PMR	N	NA	81	1.0 (0.8-1.2)	100	117
		PMR	N	NA	52	1.1 (0.8-1.4)	100	118
		SMR	L	1005	4	0.9 (0.2-2.3)	55	119
		SMR	L	5285	NR	NR (NC)	NC	120
Synthetic vitreous mineral fibre industry**	3	SMR	Y	4380	11	0.8 (0.4-1.3)	94	121
		SIR++	Y,L	3214	16	0.8 (0.4-1.3)	98	122
		SMR	Y,L	NR	NR	NR (NC)	NC	123
Telecommunications workers	2	SMR	N	867	7	0.6 (0.3-1.3)	86	124
		SMR	N	2398	5	0.9 (0.3-2.0)	62	125
Textiles and garments	6	SMR	N	923	6	NR (NC)	NC	126
		SMR	N	725	NR	NR (NC)	NC	127
		PMR	N	NA	NR	NR (NC)	NC	128
		SMR	Y,L	9022	33	0.7 (0.5-1.0)	100	129,130
		SMR	L	2724	33	1.2 (0.8-1.6)	100	131
Waitresses and bartenders	1	SIR	Y	5314	83	0.8 (0.6-1.0)	100	132
x Ray technicians, radiation workers	8	SMR	C	594	NR	NR (NC)	NC	133
		SIR	C	594	1	0.3 (0.0-1.5)	49	133
		SMR++	C	3366	21	0.7 (0.4-1.0)	100	134,135
		SMR++	N	15086	157	1.0 (0.9-1.2)	100	134,135
		SMR++	C	2598	4	1.0 (0.3-2.6)	50	136
		SMR++	N	2598	10	0.7 (0.3-1.2)	98	136
		SMR	N	677	5	0.5 (0.2-1.2)	84	137
		SIR	L	5443	11	1.4 (0.7-2.4)	76	138
		SIR++	N	NR	3	2.5 (0.6-6.8)	23	139
		SIR++	N	NR	19	0.9 (0.5-1.3)	98	139
		SMR	L,D,C	8473	NR	NR (NC)	NC	140

Table 3 continued overleaf

statistical power was above 80% in about 75% of studies, the small number of cases found indicates that the power to detect excess risks in subgroups and to test for trends in exposure was generally low.

A variety of indices of exposure or surrogates of exposure were used in these studies, but in only 10 studies^{68 102 131 134-136 155 166-168} were risks of breast cancer actually presented by level or duration of exposure.

PRINCIPAL FINDINGS

Table 4 shows the number of studies with at least one significant positive association for female breast cancer as well as the number of studies with the potential for investigating each occupational circumstance. This denominator was calculated from a baseline of 16 studies (four case-control studies⁶¹⁻⁶⁴ and 12 other independent studies based on administrative data) and, for specific occupational cir-

Table 3 continued

	Reports n	Study design	Exposure- response*	Women n	Cases n	Relative risk†95% CI	Statistical power(%)‡	Reference
Chemical and other exposures:								
Asbestos	9	SMR	Y,D	922	NR	NR (NC)	NC	141,142
		SMR	Y	284	NR	NR (NC)	NC	143
		SMR	Y,L,D,C	440	NR	NR (NC)	NC	144
		SMR	N	1327	23	1.1 (0.7-1.6)	99	145
		SMR	L	500	7	0.9 (0.4-1.8)	76	146
		SMR	N	3708	22	0.9 (0.6-1.4)	99	147
		SMR	E	657	NR	NR (NC)	NC	148
		SMR	Y	343	NR	NR (NC)	< 15	149
Benzene	1	SMR	L	1005	4	0.9 (0.2-2.3)	55	119
Chlordane	1	SMR	N	87	0	NR (NC)	NC	150
Cutting fluids	2	PMR	N	NA	NR	NR (NC)	NC	151
		SMR	Y	4680	NR	NR (NC)	NC	152
Diesel engine exhaust	1	PH(I)	E	86069	2507	1.5 (1.0-2.3)	100	153
Ethylene oxide	1	SMR	D	10040	42	0.9 (0.6-1.1)	100	154
Formaldehyde	3	SMR	D	9022	33	0.7 (0.5-1.0)	100	129,130
		SMR††	E,C	1526	10	1.0 (0.5-1.9)	84	155
		SMR‡‡	E,C	1604	12	0.8 (0.5-1.2)	100	155
Nickel-cadmium	1	SMR,PH(M)	E	466	NR	NR (NC)	NC	156
Nickel-chromium	1	SMR,PH(M)	L	1401	NR	NR (NC)	NC	157
Polychlorinated biphenyls (capacitor industry)	2	SMR	N	1309	7	1.0 (0.4-2.1)	70	158
Perfluorooctanoic acid	1	SMR	N	1556	2	NR (NC)	NC	159
Polyvinylchloride	3	SMR	Y,L	749	3	0.5 (0.1-1.5)	64	160
		C-C(M)	E	NR	44	1.8 (P > 0.05)	NC	161,162
		SMR	L	1037	0	0.0 (NC)	NC	163
Silica	2	SMR	N	13	NR	NR (NC)	NC	164
		SMR	N	NR	NR	NR (NC)	NC	165
Styrene	3	SMR	L,D,C	3868	12	0.5 (0.3-1.0)	99	166,167
		SMR	Y,C	6128	13	0.5 (0.3-0.9)	99	168
Trichloroethylene	3	SMR,SIR	E,D	249	NR	NR (NC)	NC	169,170
		SMR	C	3138	9	0.8 (0.4-1.5)	88	68
Vinyl chloride monomer	1	SMR	L	1037	0	NC (NC)	NC	163
Number of reports	106							
Number of independent studies§§	92							

All but one of the cohort studies were based on industrial populations; this one¹⁵³ included subscribers to a health insurance plan.

NA = not applicable; NC = not calculable; NR = not reported; C-C(M) = nested mortality case-control study; PH(I/M) = proportional hazards analysis of incidence (I) or mortality (M).

*Exposure-response represents the type of analyses considered by the authors of the report. However, such analyses were not necessarily reported for breast cancer. Abbreviations: N = none; L = length of employment; Y = year since first hire; S = salary/wage; E = level of exposure; D = duration of exposure; and C = cumulative exposure.

†Relative risks refer to the whole population, unless otherwise stated. For a series of reports, estimates are quoted for the latest publication.

‡Statistical power to detect a relative risk of 2 (5% level of significance) was calculated with the method of Beaumont and Breslow¹⁷¹. The expected number of cases for values of power are: 50%: 3.93 expected cases; 80%: 8.98; 90%: 12.44; and 95%: 15.72.

§An excess risk was found among women who started work before 1935 (SMR = 1.27; 95% CI: 1.01-1.57).

¶First line represents data for a cohort of union members (PMR analysis), and the second line represents a PMR analysis based on death certificates.

||First line is for wage (union) employees and second line for salary employees.

**The studies in the synthetic vitreous mineral fibre by Saracci and colleagues¹²¹ and Simonato *et al*¹²² included 13 European plants.

††Refers to exposed or monitored workers.

‡‡Refers to unexposed or unmonitored workers.

§§Non-independent studies were: United Kingdom radiation workers,¹³⁴⁻¹³⁶ Hanford workers,¹³⁹⁻¹⁴⁰ and workers in the synthetic vitreous mineral fibre industry.¹²¹⁻¹²²

cumstances, it was augmented from among other studies in which there was the possibility that these circumstances could have been investigated. These denominators should be considered to be approximate because information on the composition of the workforce, and consequently the types of occupational circumstances that could be investigated, were not usually described. In what follows, we will clarify some of the main points in table 4 and describe the more interesting results.

Clerical and professional

Associations with cancer incidence or mortality with clerical and professional jobs were reported primarily in studies based on administrative data. These studies were from widely different areas of the world, including Canada,^{24 33 35} China,⁵⁷ Denmark,^{48 53} Finland,⁵⁵ Holland,²⁵ Italy,⁴⁷ Japan,⁴⁹ Russia,²³ the United Kingdom,^{40 44 45} and the United States.^{22 27 29 46} The number of studies showing excess risks was rather striking for several occupational categories: white collar, professional and managerial occupations,^{22-24 27 29 40 44-46 48 49 53 57} clerical, secretarial, and related jobs;^{22 27 29 33 35 40 43 46 48 49 53 57} teachers;^{22 23 27 29 33 35 40 44-48 53} nurses;^{22 23 25 27 29 33 35 46 55} scientists;^{22 23 27 29 33 35 46 93} physicians and other

health professionals,^{22 23 27 29 33 35 40 44-46 48 53 55} and clergy.^{22 25 27 29 46 49}

In one case-control study,⁶¹ excess risks were found for clerical workers, for people employed in the insurance industry, but significant negative associations were also reported for people working in professional and related services, and managers and administrators. In seven cohort studies involving industrial populations,^{73 100 108 109 131 134-136 139 154} risks for a variety of administrative and secretarial or clerical occupations were not greater than expected. Also, a study of municipal workers⁹⁷ did not show any associations for any job category, including clerks, professional, and technical.

In view of the fact that exposures to specific occupational agents cannot be identified easily in most of these occupational groups, one must inquire whether methodological weaknesses, such as uncontrolled confounding, in the administrative studies produced spurious results. In particular, the effect of confounding was examined in only one PMR study.^{32 35} Here it was found that PMRs for teachers and nurses were reduced when homemakers were removed from the control group (teachers: PMR 1.68 (P < 0.05) and 1.37 (P < 0.05); nurses: PMR 1.20 (P < 0.05) and 0.99,

Table 4 Summary of the evidence linking selected occupational circumstances with breast cancer in women

Occupational circumstance	Number of studies with at least one positive significant finding				Total number of studies with the possibility of investigating the circumstance*
	Administrative	Cohort	Case-control	Total	
White collar managerial occupations and other related professions	11	0	1	12†	21
Clerical and related jobs	9	0	1	10	22
Teachers	7	0	0	7	16
Scientists	7	1	0	8	17
Nurses	7	0	0	7	17
Other health professionals	4	1	0	5	18
Clergy	3	0	0	3	16
Cosmetologists, beauticians	2	2	1	5	21
Pharmaceutical industry	1	2	0	3	19
Food industry	2	0	0	2‡	17
Textile and clothing workers	2	0	0	2§	22
Bartenders and waitresses	1	0	0	1¶	17
Furniture workers	0	1	0	1	17
Transportation industry	1	0	0	1**	16
Electronics manufacturing	1	0	0	1	17
Printing	1	0	0	1	17
Farmers, agriculture	1	0	0	1††	19
Shoe and leather	0	1	0	1	21
x Ray technicians, radiation workers	0	1	0	1	21
Laundry and dry cleaning	0	0	0	0	18
Rubber workers	0	0	0	0	22
Asbestos	0	0	0	0	24
Chemical industry (excluding petroleum manufacturing)	1	3	0	4	NE
Potential exposure to extremely low frequency electromagnetic fields	4	0	0	4	NE

Abbreviations (see also table 2): NE = not estimable.

*The baseline number of studies (16) includes: 12 studies based on administrative data^{21-27,29,30,32-35,37-39,40-46,48-50,53-57} and four case-control studies.⁶¹⁻⁶⁴ The case-control study by Franceschi *et al*⁶² focused on farmers and that of Koenig and coworkers⁶⁴ on beauticians. The number of studies above 16 are from the 92 independent cohort studies and the following studies based on administrative data: electronics,⁵¹ printing,⁵² farmers and agricultural occupations,^{31,58,60} textiles,²⁸ shoe and leather manufacturing,³⁶ health care workers,⁵⁵ and beauticians and cosmetologists.⁵⁹

†Relative risks from one case-control study (professional and related services)⁶¹ and one PMR study (domestics)³³ were significantly less than expected.

‡Excludes bartenders, waitresses, and workers in hotels and restaurants. One SIR study⁴⁸ and one SMR/PMR study⁴⁵ showed significant deficits.

§Significant negative associations were found in one PMR study,²⁸ in three SIR studies,⁴⁷⁻⁴⁹ in one case-control study,⁶³ and in one cohort study of garment workers exposed to formaldehyde.^{129,130}

¶Four studies showed significant deficits.^{29,33,34,39,132}

||The positive association was from one cohort study, and it was restricted to black women working with wood furniture⁸⁹; a significant negative association was found for white women working in all furniture industries combined.

**A significant negative association was found in one SIR study.⁴⁸

††Significant negative associations were found in two SIR studies,⁴⁹ in one PMR study among non-white women,³⁸ family workers in Denmark and farm employees in Italy,⁶⁰ and in a SIR study of Swedish reindeer herders.⁵⁸

respectively),³⁵ thus suggesting that some or all of the excess risk may be due to confounding by reproductive factors. Nevertheless, health professionals are of considerable interest because they may be exposed to a wide variety of agents, including anaesthetic gases and organic solvents.¹⁷² In the one major longitudinal study of nurses, risks of breast cancer relative to the general population have not been reported.¹⁷³ Lastly, a cohort study of scientists, laboratory technicians, and maintenance workers showed a significant increase in the risk of breast cancer (table 3).⁹³ Exposures were diverse, including radiation, solvents, chemical mutagens, and viruses.

Cosmetologists, hairdressers, and beauticians

Of the four cohort studies⁷⁸⁻⁸¹ investigating cosmetologists, two studies^{80,81} showed increased risks of about 20% (table 3). The negative results may be due to low statistical power.^{78,79} In the case-control study of Koenig *et al*,⁶⁴ a relative risk of 3.0 (95% CI 1.1-7.8) was found among beauticians employed for five or more years. Significantly increased relative risks were detected in three administrative studies: RR 1.6 (P < 0.05),²² RR 1.3 (P < 0.05),⁴⁹ and RR 1.2 (95% CI 0.9-1.6).⁵³ It is likely that cosmetologists have been exposed to several potentially toxic agents, such as organic dusts (hair), hair dyes, organic solvents (in nail products, settings, lotions,

and hair sprays), and detergents. There is little information on the carcinogenicity of most of these substances, although some organic solvents are accepted animal and human carcinogens (benzene); hair dyes do not seem to be associated with a risk of breast cancer.⁶⁴

Pharmaceutical industry

Positive associations were found in two cohort studies of pharmaceutical workers (table 3).^{100,102} There was a suggestion that incidence rates increased by duration of service among workers involved in the manufacture of insulin, sex hormones, and other pharmaceutical products.¹⁰² Confounding by reproductive factors may not be an important issue in this study, as current plant personnel and the general population were shown to have similar distributions of number of children, age of mother at first birth, age at menarche, and body mass index. However, a significantly higher frequency of oral contraceptive use, a weak risk factor for breast cancer, and a slightly higher use of non-contraceptive sex hormones were found among workers. No associations were found in the investigation of pharmacy technicians¹⁰¹ and in the case-control studies, and one study based on administrative data showed an excess risk among black women working in the pharmaceutical industry (RR 1.6, P < 0.05).⁵⁰ The discrepant findings in the studies of pharmacy technicians and pharmaceutical manufactur-

Table 5 Relative risks of female breast cancer in relation to occupations with potential exposure to extremely low frequency electromagnetic fields

Type of study based on administrative data	Reference	Occupation or industry	Relative risk	95% CI or P value
SMR	22	White women, telephone operators	1.7	P < 0.05
SMR	23	Communication	2.9	1.7–4.6
PMR	40	Telephone operators	1.3	P < 0.05
MOR	42*	Electrical engineers	1.7	0.9–3.3
		Electrical technicians	1.3	0.8–2.1
		Telephone installers, repairers, line workers	2.2	1.2–4.0
		Other "electrical occupations"	0.7	0.4–1.3
MOR	43*	Telephone industry		
		White women	1.4	1.3–1.5
		Black women	2.2	1.6–3.1
		Black and white women combined		
		Office workers	2.5	1.8–3.5
		Telephone operators	0.9	0.5–1.6
		Engineers and technicians	2.7	1.3–6.0
SMR	51	Telecommunications industry	0.6	0.3–1.3
SIR	56	Exposure to intermittent magnetic field (> 0.3 μ T)	1.0	0.9–1.0
		Exposure to continuous magnetic field (> 0.3 μ T)	0.9	0.7–1.2

In tables 5 and 6, relative risks for all cohort studies are presented, as well as those studies based on administrative data in which excess relative risks (lower confidence limit ≥ 0.9) were found. When CIs were not presented but observed and expected numbers were available, 95% CIs were calculated by us assuming a Poisson distribution. Otherwise the original P values are shown.

*References 42 and 43 were based on the same data.

ing workers are most simply explained by the fact that technicians are not likely to be exposed to the same extent as manufacturing workers.

Textiles and clothing

No associations were found in the two small cotton textile manufacturing cohort studies,^{126 127} among textile workers, dyers and bleachers,¹²⁸ and among workers manufacturing synthetic fibres and textiles (mostly cellulose acetate)¹³¹ (table 3). There were no associations with formaldehyde exposure in the study of garment workers.^{129 130} In one case-control study, significant deficits were found among workers in the textile mill industry,⁶³ and no associations were reported in the other case-control studies.^{61 62 64} Two studies based on regularly collected data showed excess risks,^{44 45 53} and significant deficits were found in four other studies.^{28 47–49}

Radiation workers and x ray film technicians

Six cohort studies have been conducted among radiation workers, including diagnostic x ray film personnel,¹³⁸ workers at a uranium fuel fabrication plant,¹³³ a thorium processing plant,¹³⁷ United Kingdom Atomic Energy Authority plants,^{134 135} the Sellafield reprocessing plant,¹³⁶ and the Hanford site in Washington state^{139 140} (table 3). Exposures across the studies were quite varied, including whole body ionising radiation as well as exposure to radionuclides. Despite the fact that ionising radiation is a recognised risk factor for breast cancer,⁵ none of these studies showed any excess risks.

Potential exposure to extremely low frequency electromagnetic fields

In 1987, Stevens¹⁷⁴ suggested that breast cancer may be caused by exposure to extremely low frequency electromagnetic fields. It was

suggested that these fields would reduce pineal melatonin production, thereby allowing levels of oestrogen and prolactin to increase. Thus, extremely low frequency electromagnetic fields indirectly may affect hormonal secretions thereby increasing the risk of breast cancer. This hypothesis has stimulated much debate, but few epidemiological studies have been carried out among women. Four studies of male breast cancer^{175–178} have shown associations with employment in "electrical occupations". The only reports on female breast cancer derive from six administrative studies^{22 23 40 42 43 51 56} of which four have shown associations with a variety of electrical occupations^{22 23 40 42 43} (table 5).

Chemists and chemical workers

Higher than expected risks among chemists were found in MOR analyses of two cohorts,^{72 74} with considerably higher risks noted in single women (MOR 2.3, 95% CI 1.5–3.5).⁷² For chemical manufacturing workers, higher than expected incidence rates of breast cancer were found among Du Pont company workers^{75 76}; there were higher risks among salaried workers (SMR 1.3) than among those paid on an hourly basis (SMR 0.9). No associations were found among Dow Chemical⁷³ or Union Carbide workers.⁷⁷ A difficulty in interpreting these studies is that workers were most likely exposed at various levels to a wide array of chemical agents. It is therefore unclear how to interpret the findings between salaried staff and hourly wage earners. One PIR study⁵⁰ showed increased risks among black women working in the chemical industry (RR 1.4; P < 0.05), and no positive associations with general chemical occupations were reported in the case-control studies.

Other specific chemical exposures have been investigated (table 3), with negative results reported for women exposed to chlori-

Table 6 Relative risks of female breast cancer in relation to occupations with potential exposure to organic solvents

Type of study	Reference	Occupation, industry, or exposure	Relative risk	95% CI or P value
Cohort	68	Aircraft maintenance workers	0.7	0.5-1.0
		Exposed to trichloroethylene (no trend for cumulative exposure)	0.8	0.4-1.5
		Exposed to freon	3.1	1.2-6.4
		Exposed to solder flux	3.1	1.1-6.7
		Exposed to isopropyl alcohol	3.1	1.3-6.4
Cohort	82,83	Dry cleaners		
		Entire cohort	1.1	0.6-1.7
		Perchloroethylene only subcohort	1.0	0.4-2.2
		Perchloroethylene and other exposures	1.1	0.6-1.9
Cohort	84,85	Dry cleaners	1.0	0.7-1.4
Cohort	86	Lamp manufacturing (coiling/wire drawing) > 6 months employment	2.0	0.9-4.0
		(Possible exposure to methylene chloride and trichloroethylene.)		
Cohort	94	Leather tannery workers		
		Incidence		
		No latency period	1.3	0.8-2.0
		≥ 20 years latency	1.5	0.9-2.3
Cohort	119	Shoe manufacturing (Exposure to benzene and other solvents.)	0.9	0.2-2.3
Cohort	120	Shoe manufacturing (Exposure to toluene and other solvents.)	NR	
Cohort	129,130	Garment workers exposed to formaldehyde	0.7	0.5-1.0
Cohort*	161,162	Polyvinylchloride workers	1.8	P > 0.05
Cohort	166,167	Styrene exposed workers	0.5	0.3-1.0
Cohort	168	Styrene exposed workers	0.5	0.3-0.9
Cohort	169,170	Trichloroethylene exposed workers	NR	
C-C	61	Miscellaneous manufacturing industry	0.6	P < 0.01
		Operators in fabricated metal	0.5	P = 0.04
		Operators in printing and publishing	0.4	P = 0.03
		Operators in leather industry	1.2	P > 0.05
Studies based on administrative data:				
SMR	24	Printing and publishing	2.2	1.1-3.9
SMR (< 50)†	45	All others in painting, repetitive assembling, product inspection, packaging and related	1.5	0.9-2.2
PMR (≥ 60)†	45	All others in painting, repetitive assembling, product inspection, packaging and related	1.4	0.9-2.0
MOR	46	WW, mechanics and repairers	1.7	1.2-2.4
PMR		WW, precision production	1.0	P > 0.05
MOR		WW, precision production	1.1	1.0-1.2
PMR		BW, precision production	1.2	P < 0.05
PIR	50	BW, printing industry	1.8	P < 0.05
SIR	53	Bookbinder's assistant	1.5	0.9-2.3
		Self employed/iron-metal industry	2.9	1.0-6.8
		Self employed/photographic studios	2.3	0.6-6.0

WW = White women; BW = black women. See previous tables for other abbreviations.

*Case-control analysis of the cohort.

†Numbers in parentheses represent ages of subjects. Married women were excluded from consideration.

nated naphthalenes in the cable manufacturing industry,⁷¹ workers exposed to ethylene oxide,¹⁵⁴ and rubber manufacturing workers.^{108-110 113} A positive association was found among women potentially exposed to diesel engine exhaust.¹⁵³

Potential exposure to organic solvents

We have hypothesised (Labrèche and Goldberg, submitted for publication)¹⁷⁹ that exposure to organic solvents may be associated with an increased risk of breast cancer. The suggested mechanism is through migration of these lipophilic substances, and their metabolites, to adipose tissue in the breast where they can be stored, absorbed into the apocrine glands, possibly biotransformed, and then excreted into the ductal systems where they may remain in contact with the parenchyma for considerable amounts of time, thereby initiating or promoting carcinogenesis. There are experimental data that suggest that some organic solvents are carcinogenic in rats and mice (benzene, 1,2-dibromoethane, 1,1-dichloroethane, 1,2-dichloroethane, methylene chloride (benign tumours), styrene, 1,2,3-trichloropropane, and vinyl chloride).^{180 181}

Table 6 shows that the epidemiological data are rather sparse. Of interest are workers in

laundry and dry cleaning establishments who have been exposed to several organic solvents. Stoddard solvent was used until the 1930s, after which carbon tetrachloride became the mainstay.^{82 85} Perchloroethylene slowly replaced the earlier solvents between the 1940s and the 1960s. Trichloroethylene and, more recently, fluorocarbons have been used. According to Brown and Kaplan,⁸² by 1977, 74% of the industry used perchloroethylene, 24% used petroleum based solvents, and about 2% used fluorocarbons. No increased risks of breast cancer were noted among workers exposed to perchloroethylene,^{82 83} or to a mixture of solvents, including Stoddard solvent, perchloroethylene, trichloroethylene, and fluorocarbons.⁸⁵ None of the case-control studies nor those studies based on administrative data showed any increased risks.

The mortality study by Spirtas *et al*⁶⁸ of aircraft maintenance workers exposed to trichloroethylene was consistent with the null results from the studies of dry cleaners. Excess risks were found, however, for exposure to freons, solder flux, and isopropyl alcohol. These substances were highly correlated and it was not possible to disentangle individual effects. Axelson and coworkers^{169 170} also investigated cancer incidence and mortality in workers

exposed to trichloroethylene. No risk estimates were provided for cancer of the breast, and one must assume that very few cases were found. Incidence of breast cancer was in excess among women employed in coiling and wire drawing⁸⁶ in the manufacturing of lamps, in which methylene chloride and trichloroethylene were probably used.

Two cohort studies of female shoe manufacturers have been carried out.^{119 120} Exposures included organic solvents and solvent based adhesives; in the study by Paci *et al*¹¹⁹ benzene was originally an important component of glues used before the mid-1960s (up to 70% by weight) and may have been an impurity in the investigation by Walker and colleagues.¹²⁰ Other solvents used typically were toluene, hexane, methyl ethyl ketone, and acetone in concentrations ranging from 10 ppm to 330 ppm.¹²⁰ The small study by Paci *et al*¹¹⁹ showed no increased risks, and in the larger American study¹²⁰ risk estimates were not reported for cancer of the breast.

Mikoczy and coworkers conducted a cohort study of leather tannery workers exposed to several compounds,⁹⁴ including benzene and other chlorinated solvents, and found incidence rates to be between 30% and 50% above those expected. A case-control study in a small cohort of polyvinyl chloride workers showed a non-significantly increased risk of death from breast cancer (OR 1.8).^{161 162} No associations were found among workers exposed to styrene.¹⁶⁶⁻¹⁶⁸ Lastly, among the studies based on administrative records, there have been suggestions of increased risks for certain occupations that may involve exposures to solvents (printing, publishing, mechanics).^{24 45 46 50 53}

Discussion and conclusions

This review has summarised results from occupational investigations of female breast cancer carried out within the past 25 years. Our perspective on investigations based on routinely collected data is that they may convey spurious conclusions if used by themselves, although they can be used for generating hypotheses or providing additional information to that obtained from cohort and case-control studies. The reason for treating the administrative studies in this way is their inherent limitations,^{33 182 183} including: (1) misclassification of disease status leading to reductions in statistical power and attenuation of risk ratios. Mortality data are more susceptible to these types of problems than incidence data.¹⁸⁴⁻¹⁸⁷ Moreover, because of the relatively long survival rates for breast cancer, statistical power would be further reduced in mortality studies because of an underascertainment of cases. (2) Misclassification of exposure through the use of coarse occupational categories will also lead to a loss of statistical power and an attenuation of risk ratios.¹⁸⁸ In the studies we reviewed, exposure was usually classified in terms of the last occupation (or industry) that the subject had had, or the occupation of the longest duration. This can

also lead to bias, possibly away from the null, if workers changed occupations because of illness. Notable exceptions were the Chinese study by Zheng and coworkers,⁵⁷ in which occupational histories were obtained directly from subjects (although denominators were based on census data), and the longitudinal studies from Canada,²⁴ Italy,⁴⁷ Denmark,^{48 53 56} Sweden,^{51 52 58} and Finland⁵⁵ in which occupations from censuses or labour surveys²⁴ were linked with subsequent cancer incidence or mortality data. (These were not considered as cohort studies in this report because person-years of observation by occupation at the time of enumeration were not calculable.) (3) Inability to account for key confounding factors may lead to incorrect inferences. Important risk factors for breast cancer were not accounted for in any of the investigations based on administrative data. That incorrect conclusions may be drawn from administrative studies is exemplified by the observation that although increased risks of developing breast cancer for clerical and white collar jobs were found in studies using administrative data, no associations were found in the cohort or case-control studies. It is possible that the studies of exposure to extremely low frequency electromagnetic fields, also based on routinely collected data, were biased.¹⁸³ (4) No estimates of risk by duration of employment, latency, or other indices of exposure-response were presented, thus making it difficult to assess the veracity of the associations.

Thus, we relied whenever possible on information from cohort and case-control studies, that we considered to be more robust. Nevertheless, because few studies were designed specifically to investigate risks of breast cancer, the limitations inherent in these studies must be recognised when interpreting the data. In particular, statistical power and risk estimates would have been reduced in mortality studies in which broad occupational groups were used as surrogates for exposure. As well, statistical power was generally quite low for assessing trends or for assessing risks in subgroups.

Also, confounding by reproductive factors may have affected some of the cohort studies. For example, in the studies of chemists and chemical workers higher risks were found among clerical workers⁷³ and among salaried workers⁷⁵⁻⁷⁷ than among hourly paid workers. On the other hand, no great differences for a variety of risk factors were found between workers and the general population in the one cohort study in which confounding was assessed indirectly.¹⁰²

It has been suggested that removing homemakers from reference populations will partly control for the confounding influence of reproductive and related factors.^{32 35} This has been applied to studies based on administrative data, but could also be implemented in case-control studies in which confounding variables are not measured. In the analyses of cohort studies that used mortality rates derived from the general population as the reference, homemakers can also be eliminated if occupational

information has been captured on death certificates.

One would expect in cohort studies that misclassification of exposure would be less pronounced than in studies with routinely collected data because job titles from plants should be more homogeneous for exposure. Nevertheless, exposures were ascertained in but a handful of studies. In the case-control studies, although detailed information on occupational lifetime histories was obtained directly from subjects, broad occupational groupings were reported in the analyses, with main lifetime occupation used in two studies,^{61,62} ever employed or employed for more than five years used in another study,⁶³ and duration of employment reported in one study.⁶⁴ In this last study,⁶⁴ important confounding variables for risk of breast cancer were accounted for.

Selection into and out of work among subjects enrolled in cohort studies (the healthy worker effect¹⁸⁹) may also have led to underestimation of risks. It is difficult to control for these effects, although partial control of selection into the cohort can be achieved through the use of internal control groups. However, no studies reported such analyses for breast cancer, although they were carried out for other endpoints in several studies.^{131 133-136 139 153 156 157 163 168}

Bearing in mind these limitations, we conclude that there is little support for an association between female breast cancer and employment in the textile and garment industries. The studies of cosmetologists and beauticians and of pharmaceutical manufacturing workers can be regarded as providing limited evidence in favour of an association, but further studies are required before conclusions can be drawn. Although nuclear workers are exposed to ionising radiation, a recognised risk factor for breast cancer, no associations were found. In the absence of bias, it is likely that either the length of follow up or the doses incurred were not sufficiently high to induce any observable excess risks.

There are insufficient data to make any inferences about women employed as chemists or exposed occupationally to extremely low frequency electromagnetic fields. Because of the apparent heterogeneity of exposures among workers included in the cohort studies at the large chemical companies,^{73 75-77} it is difficult to draw any conclusions from these studies. However, the few studies carried out on specific occupational agents have not provided any evidence of associations. In particular, although we have postulated that exposure to organic solvents may increase the risk of developing breast cancer, with some evidence provided from animal carcinogenicity studies, increased risks have not been found among dry cleaning workers, those exposed to trichloroethylene, or shoe manufacturers. Studies of organic solvents may, however, be beset with health related differential selection into and out of work arising from pervasive early onset toxic effects (dermatitis, hepatic and renal toxicity, central nervous system

depression, peripheral neuropathy).¹⁹⁰ Thus, there will be a selection bias if susceptible or sensitive workers are at higher risk of developing breast cancer and are more likely to leave exposed jobs early so they are less highly exposed than insensitive people. In any event, as few organic solvents have been studied adequately, including the agents already mentioned, no conclusions on the relation between organic solvents and risk of female breast cancer can be made.

It is clear from this review that few high quality studies directed specifically toward assessing occupational risks of breast cancer have been carried out to allow one to identify unambiguously occupational risk factors for breast cancer. The fact that the cohorts of women were generally small is understandable, as few women would have been in the workforce during the period covered by many of these retrospective studies. It is now feasible to carry out more detailed investigations. Juxtaposing job exposure matrices to already completed cohort or case-control studies¹⁹¹ will provide a cost effective method to study occupational exposures. Also, population based, case-control studies, with approaches similar to those developed by Siemiatycki *et al*, Gérin *et al*, and Stewart *et al*,^{182 192-194} although more expensive, should provide high quality data to investigate occupational risk factors. In fact, we are now carrying out such an investigation in Montreal. Cohort studies of specific industrial populations can then be carried out to follow up promising leads from the case-control studies.

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