

Chapter 3 — Solid Tumours

Brief Methodology

Nine solid tumours were chosen for study in this review, using data from the Canadian Cancer Statistics webpage on cancer incidence, potential years of life lost and percent change in age-standardized incidence for selected cancer sites. (See Chapter 2 – Methods for a detailed description). From these lists the following solid tumours were selected to be included in this review: lung cancer, breast cancer, pancreatic cancer, brain cancer, prostate cancer, stomach cancer, ovarian cancer, and kidney cancer. Testicular cancer was also selected, but the one retrieved article was of such poor methodological quality that it was excluded from the review. Colorectal cancer was also a tumour of interest, but despite numerous searches, no primary studies of pesticide exposure and bowel cancer were found.

General Strengths and Weaknesses in Study Design

Most of the solid tumour primary studies share common methodological strengths and weaknesses. There are several well-designed studies that include large sample sizes with an extensive follow-up period. Although the majority of the studies in this area are cohort or case-control, there are a few ecological studies, and they have also been included in this review.

The studies investigated a variety of populations including farmers, aerial pesticide applicators, children of pesticide applicators and employees of pesticide production plants. A small number of studies look at household and garden pesticide exposure. The exposures under study vary from pesticides as a general exposure category, to sub-categories of pesticides (i.e. fungicides, herbicides, insecticides), to specific pesticides. For the case-control studies, exposure was typically assessed through questionnaires regarding occupational and/or home exposure. Usually an industrial hygienist assigned categories of exposure based on the questionnaire answers. The cohort studies relied on agricultural census data and pesticide application licenses to assess exposure. However, the major drawback to most of the poorer quality papers is that the proxy measure of exposure is poor, introducing the possibility that the study results may be biased. In addition, several of the weaker papers do not sufficiently consider the broad range of potential confounders that are necessary to investigate (particularly in the breast cancer papers where several ignore important covariates like age at menarche, menopause, reproductive history, history of breast cancer in the family, etc). However, for the most part, the solid tumour studies evaluated in this review are of moderate to good quality, and present interesting and clinically relevant findings regarding the relationship between pesticide exposure and solid tumour cancers.

Brain Cancer

This review included eleven papers (14–24) that investigated the association between pesticide exposure and the risk of brain cancer. Of these studies, seven looked specifically at brain cancer as an outcome; one at intracranial gliomas, and another at astrocytoma and PNET (primitive neuroectodermal tumours) while the other four considered all cancers in general. Of the eleven studies, five were case-control, five cohort, and one ecological. The studies include populations in the US, Canada, and Europe and all were considered of good methodological quality, with global rankings of four or above.

The cohort studies all found significant positive associations between pesticide exposure and brain cancer. One study included a large sample size of 323,292 offspring of Norwegian farmholders and used census data to develop an exposure proxy through pesticide and spray equipment purchase (17). Increased risk was found for brain tumours, in particular non-astrocytic neuroepithelial tumours. In addition, there was a dose-response relationship with the magnitude of the effect strongest in children aged 0 to 14 years. The case-control studies found similar results. With regards to household pesticide use, another good quality study found a significant positive association between risk of pediatric brain tumours and prenatal use of flea-tick products (OR 1.7, CI 1.1-2.6) (20).

Breast Cancer

For the breast cancer group, twelve articles were found using the search strategy. Of these, four were excluded because they were lab studies rather than studies about human populations, and two others were excluded on quality scores. The remaining six papers include one cohort study with non-exposed controls, two case-controls, and three ecological studies. The cohort study (27) followed a group of women with at least ten years' work in greenhouses for more than four hours daily. Mammographic findings were compared between exposed women and matched, non-exposed women who were residents of large towns with non-agricultural occupations. The exposed women were found to be at a higher risk of having mammographic findings that are risk markers for the development of breast cancer. However, there was not a statistically significant difference between the groups in findings of malignancies following biopsy and histological confirmation.

Of the two case-control studies, two present positive associations, and the other two (excluded) found no association. One population-based study interviewed 1018 women with incident breast cancer, identified from the British Columbia Cancer Registry (26). Using interview information, occupations were coded in an effort to assess exposure to a variety of chemicals, one of which included pesticides. Excess risk of breast cancer was found in crop farmers and in the fruit and vegetable industries. Another case-control study focused specifically on farming and incident breast cancer (28). After controlling for a large number of potential confounders, this study concludes that among women who farmed, ORs were elevated for those who reported being present in fields during or shortly after pesticide application (OR 1.8, 95% CI 1.1-2.8) and for those who reported not using protective clothing while applying pesticides (OR 2.0, 95% CI 1.0-4.3). Interestingly, an increased duration of farming was associated inversely with breast cancer risk. Possible mechanisms for this may include a protective effect of physical activity against breast cancer, exposure to sunlight, which may increase vitamin D levels and thus decrease breast cancer risk, or the possibility that some pesticides or contaminants (like TCDD) may possess antiestrogenic activity.

Of the three ecological studies of breast cancer, one examined a mixed pesticide exposure, and the other two looked at herbicides only. The former study used National Cancer Institute data and focused on the whole population of Mississippi (25). The total number of acres planted during 1997–2000 for each Statistical Economic Area and by type of crop was used as a proxy measure for pesticide exposure. The total number of acres planted was positively and statistically significantly associated with breast cancer mortality rate. Specifically, the strongest correlations were associated with rice crops and catfish crops. The authors suggest that this may be due to pesticide bioaccumulation through the food chain. The other two ecological studies consider exposure to herbicides, specifically atrazine and triazine. Both of these study populations are the residents of the state of Kentucky and are part of the same research group, so it is likely that

these papers present information about the same study population (29, 30). While the results did not support a relationship between exposure to atrazine and breast cancer incidence (29), there was a statistically significant positive association with triazine exposure (30); specifically, there was an increased breast cancer incidence with medium and high levels of triazine herbicide exposure (OR 1.14, $p < 0.0001$ and OR 1.2, $p < 0.0001$ respectively).

Kidney Cancer

Seven papers evaluated the relationship between kidney cancer and pesticide exposure. However, one of these was excluded due to its poor methodological quality. Of the remaining six studies, four are case-control, and two are cohort studies. One of the cohort studies looked at kidney cancer mortality in a large retrospective cohort of 167,703 children (32). A statistically significant excess of kidney cancer was found among the offspring of men with potential occupational exposure to pesticides (PMR 1.59, 95% CI 1.18-2.15). The other cohort study assessed the relationship between occupational exposure to pentachlorophenol and cause of mortality at a chemical company that produced this pesticide (35). It also found a statistically significant positive association between exposure and death from kidney cancer (SMR 502, 95% CI 101-1468). Unfortunately, the confidence intervals are quite broad in this latter study due to the small numbers in the group.

The four case-control studies all found statistically significant positive associations between pesticide exposure and kidney cancer (31, 33, 34, 36). This effect was seen most consistently for longer duration of exposure, and found in the cases of children whose parents were occupationally exposed to pesticides.

Lung Cancer

Four studies examined the association between lung cancer and pesticide exposure. Of these, two looked specifically at lung cancer mortality and incidence, and two considered all types of cancer mortality. One of the latter two is a retrospective cohort study of male farm workers in Italy who obtained a license to handle pesticides during the period 1973–1979 (38). The authors conclude that this cohort actually had a lower risk of mortality due to lung cancer when compared to provincial and national mortality data. This lowered risk was attributed to the ‘healthy worker effect,’ or the possibility that smoking is less common among farmers. Smoking status was not measured in the study. Given the clear relationship between smoking and lung cancer, the absence of information on this important covariate limits the usefulness of the study’s findings. The other cohort paper considered all causes of mortality in a cohort of golf superintendents (39). Conversely, they found an elevated PMR (proportionate mortality ratio) of lung cancer in the exposed cohort. However, they also failed to control for smoking or passive smoking exposure and thus it is difficult to assess any potential causal relationship between the two.

The other two papers, case-control studies, included smoking as an important covariate in the analysis. One examined the occupationally related risk of lung cancer among non-smoking women for several occupations (37). Of these occupations, pesticide exposure was considered as a specific exposure in the workplace. An elevated incidence of lung cancer was found for women exposed to pesticides when compared to a population-based sample of controls (OR 2.4, 95% CI 1.1-5.6). A dose-response relationship was also found where the higher exposure range had a higher risk of lung cancer when compared to the lower exposure range. The other case-control study was nested within a retrospective cohort of Florida pest control workers (40), and considered specific types of pesticides, rather than the broad category as in the other two studies.

This study looked at lung cancer mortality, rather than incidence, as the outcome of interest. Information regarding specific pesticide use was collected from proxy interviews of next-of-kin and included information regarding use of organophosphates, organochlorines, carbamates, inorganics, organobromides, natural products, and phenoxy herbicides. Results were provided for comparisons between cases and dead controls and cases and living controls. Of these results, there was a statistically significant increased risk of lung cancer mortality for carbamate use in cases versus dead controls (OR 16.3, 95% CI 2.2-122.5) and for phenoxyacetic acid use in cases versus living controls (OR 22.4, 95% CI 1.8-276.2). Unfortunately, the confidence interval ranges for these values are quite broad, making it difficult to assess the precision of this value. Although increased risks were also found for the use of organophosphate, organochlorine, and inorganics, these findings were not statistically significant.

The results from these studies suggest that there may be a relationship between some pesticide exposures and risk of lung cancer. However, there is a need for further studies in this area that consider smoking and passive smoking exposure as important covariates before any causal associations can be concluded.

Ovarian Cancer

The current literature review failed to find any studies that looked exclusively at ovarian cancer. Rather, there was a selection of papers that considered ovarian cancer in addition to several other solid tumour cancers. One of these actually found a negative association between ovarian cancer and atrazine exposure (41). However, this suggested protective effect on incident ovarian cancer was not statistically significant, and determined in the context of an ecological study. Thus, its findings are limited in making associations between ovarian cancer risk and atrazine exposure.

Pancreatic Cancer

The risk of pancreatic cancer and exposure to pesticides was evaluated in three studies; two case-control, and one cohort. All the papers found a positive association, particularly for high intensity exposure, and exposure to herbicides and fungicides.

The retrospective cohort study followed male aerial pesticide applicators for their cause of death (43). This large study found a statistically significant positive association of pancreatic cancer in the applicator group when compared to non-exposed individuals (SMR 2.71, 95% CI 1.4–5.3). Unfortunately, the study did not consider smoking as a potential covariate.

The two case-control studies also found positive significant associations, and one of these included smoking habits as an important covariate. One Spanish study (42) compared incident cases of pancreatic cancer with hospital controls. Occupational history was obtained through interview and exposures evaluated by industrial hygienists. Moderately increased ORs were found in the high-intensity category of pesticides, highest for arsenical pesticides (OR 3.4, 95% CI 0.9–12.0) and ‘other pesticides’ (OR 3.17, 95% CI 1.1–9.2). The other case-control study, conducted in the United States (44, 45) compared pancreatic cancer cases with a random sample from the population. Occupational information was also collected through interviews, and then a job-exposure matrix was used to estimate the level of occupational risk for pesticide exposure. Excess risks were found for occupational exposure to fungicides (OR 1.5, 95% CI 0.3–7.6) and herbicides (OR 1.6, 95% CI 0.7–3.4).

Prostate Cancer

Ten papers looked at the risk of prostate cancer with exposure to pesticides. However, two were excluded due to poor methodological quality. Of the remaining eight papers, five are cohort studies, two case-controls, and one ecological (46–53). An excellent study (46) investigated a cohort of 55,332 male pesticide applicators and found a positive statistically significant association between exposure to pesticides and prostate cancer when compared to the rest of the population. This increase was also evident with the use of methyl bromide and use of chlorinated pesticides among applicators over 50 years of age (OR up to 3.75, $p < 0.004$) (46). The other studies present a similar trend, suggesting that pesticide exposure, particularly at high levels of exposure, is a risk factor for the development of prostate cancer.

Stomach Cancer

One paper from Ontario investigated the relationship between exposure to nitrate and atrazine and stomach cancer (54). Although they found a positive significant association between atrazine contamination levels and stomach cancer ($p < 0.05$), this study was an ecological design, and therefore it is difficult to make any conclusions from this about causality. Nevertheless, it is interesting for forming hypotheses about this new and yet to be studied area.

General Conclusions

In summary, there are many studies showing positive associations between solid tumours and pesticide exposure. In particular, the large well-designed cohort studies consistently show statistically significant positive associations. The relationships are most consistent for high exposure levels such as those found in occupational settings. The results frequently show dose-response relationships, and quality of studies was generally good. Overall, these findings strongly support a reduction of pesticide use, particularly for those individuals with occupational exposure (agriculture, pesticide applicators) at high doses. Future work targeted at non-occupational exposures, in addition to further work on some of the less studied solid tumours is warranted and will provide continued direction for clinical practice.

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Tables

Table 1 Brain Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Cohort Studies						
Figa-Talamanca 1993	Retrospective cohort study of a group of 2310 male farm workers (over the age of 15 yrs) who were licensed to handle pesticides in Italy; included those issued pesticides licenses between 1973–1979.	Mixed pesticide exposure; mostly assessed through license information – a small group filled out a questionnaire (but did not have info on quantity or type of pesticide – just use or not).	Age	SMR, Poisson	There was a statistically significant excess for brain cancer in the exposed group (SMR 270, CI 108.6–556.9); no other ORs for brain cancer provided.	4,4
Kross 1996	Retrospective cohort study of a group of 686 deceased white male members of the Golf Superintendents Association of America; compared to white male US population; included subjects from across the US	Mixed pesticide exposure; could not provide specific exposure information as data source was death certificates; exposure assumed through membership in association.	None	PMR	The cohort experienced higher mortality for all cancers (PMR 136, CI 121, 152), PMR lung cancer 117 (CI 93, 148), PMR brain 234 (CI 121, 454), PMR NHL 237 (CI 137, 410), PMR prostate 293 (CI 187, 460).	4,4
Kristensen 1996	Retrospective cohort study of 323, 292 offspring of parents identified as farm holders in Norway born between 1952–1991.	Mixed pesticide exposure; assessed from Agricultural Censuses that had info re: pesticide purchases and pesticide spraying equipment.	Age, gender, period of follow-up, geographical region, type of agricultural work done by parent.	RR, Poisson	Positive association between brain tumours and pesticide purchase (RR 1.71, CI 1.11–2.63) and non-astrocytic neuroepithelial tumours (RR 3.37, CI 1.63–6.94); RRs for brain tumours ranged between 1.29–1.59 for various types of farming.	6,6
Littorin 1993	Retrospective cohort study of 2370 subjects who had been members of a	Mixed pesticide exposure; assessed through membership lists and	Gender, age	SMR,	This population had an increased rate of brain	4,4

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
	horticulturists' trade association between 1965-1982 in Sweden; men and women.	association records.		Poisson	tumours (SMR 3.2, CI 1.6-5.7) for young and middle-aged horticulturists; no dose response relationship.	
Smith-Rooker 1992	Descriptive cohort study (retrospective chart review) of patients enrolled in a brain tumour treatment program in Arkansas between 1984–1991 (n=100).	Herbicide exposure assessed by residence proximity to rice and cotton crops;	Age, gender, residence, occupation	% of total cases who live in areas of high rice acreage, cotton acreage; also % of cases with certain occupations	More than one third of cases came from 3 counties (these counties are high producers of cotton, rice, and wood which is associated with high herbicide use).	4,4

Case-Control Studies

Davis 1993	Case-control study to examine the relationship between childhood brain cancer and household pesticide use in Missouri; 45 cases (from age 0-10) diagnosed between 1985-1989, 85 friend controls, 108 other cancer controls; study limited to white children.	Pesticides for 'nuisance' pests (roaches, ants, spiders, termites, lice, fleas, ticks, garden or orchard pests, weeds in garden); assessed through a questionnaire administered to mother; composite variable of exposure developed for use up to age of diagnosis and # of times used during pregnancy and up to age of diagnosis.	Age, gender, child's age at diagnosis, child's exposure to environmental tobacco smoke, during birth to six months and 7 months to diagnosis, family income, fathers education, mothers education, family member in construction industry.	OR, Mantel-Hanzel	There were several positive associations of brain cancer and certain pesticides: Overall OR 3.4 (CI 1.1–10.6) for pesticide use in general during the 7 months of age to diagnosis period; other significant positive findings for use of no-pests strips, pesticides to control termites, Kwell shampoo, flea collars on pets, herbicides where ORs ranged between 0.6–6.2.	5,5
Efird 2003	International case-control study to examine farm-related exposure and childhood brain cancer; seven countries; cases under 20 yrs age at	Pesticides classified as a general term; assessed through a questionnaire administered to the birth mother about farm exposures (lots of	Age, gender, centre, race, mother's	OR, logistic regression.	Increased OR for brain tumours in children and specific farm-related exposures; pesticides OR	5,6

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
	diagnosis, diagnosed between 1976–1994; 1218 cases and 2223 controls.	info collected about different animal exposures).	education.		2.0, (CI 1.2, 3.2); no other ORs for pesticides provided.	
Pogoda 1997	Case control study of paediatric brain tumours in LA, California (age 19 or under at diagnosis); 224 cases and 218 controls.	Mixed pesticide exposure; a variety of 'nuisance' pesticides investigated; detailed questions regarding exposure during pregnancy and childhood.	Gender, age, race, mother's education, SES	OR, logistic regression	Significant positive association between brain tumours and prenatal use of flea-tick products (OR 1.7, CI 1.1–2.6); other prenatal pesticide exposures non signif, but ORs ranged between 0.9–2.7; none of the pesticide exposures were significant for childhood exposure.	5,5
Rodvall 1996	Case control study of all newly diagnosed intracranial gliomas in 25–74 yr old people living in Sweden; 192 cases and 192 controls.	Mixed pesticides exposure; questionnaire; questions about job title, industrial exposures, how many days, weeks, months, yrs, came into contact.	Gender, age, parish, social status, education	RR, logistic regression	Pesticide use in any occupation resulted in increased risk of gliomas (RR 1.8, CI 0.6–5.1 for men and RR 2.2, CI 0.5–10.5 for women).	4,4
Van Wijngaarden 2003	Case control study of to determine risk of brain cancer in relation to parental occupation; 154 astrocytoma, 158 PNET, and 312 controls in Canada and the US diagnosed between 1986–1989; cases diagnosed before the age of 6 yrs.	Four broad classes of pesticides: insecticides, herbicides, agricultural and nonagricultural fungicides; exposure assessed through a questionnaire; detailed questions about occupation and then industrial hygienist assigned exposure intensity, probability, and frequency to each parent.	Mother's education, SES, maternal age at birth	OR, logistic regression	Slightly elevated risk of astrocytoma for all four classes of pesticides (OR 1.4–1.6); for mothers elevated risk with insecticides (OR 1.9, CI 1.1–3.3), herbicides (OR 1.3, CI 0.5–3.7), and nonagricultural fungicides (OR 1.6, CI 0.9–2.7).	5,5
Ecological Studies						
Viel 1998	Ecological study; included the total population of certain areas of France (close to 600 000); male farmers and	Mixed pesticide exposure; assessed through the Pesticide Exposure Index that assesses farmers exposure at a geographical level by using agricultural	Age, income	SMR, RR, Poisson	Mortality from brain cancer among farmers was significantly higher then mortality for the overall pop	5,6

Reference

Population Description

farm laborers aged 35–74.

Pesticides Type and Exposure Assessment

and national census data.

Covariates

Statistical Analysis

Measures of Association and Values

(SMR 1.25, $p < 0.01$); significantly link between pesticide exposure in vineyards (RR 1.1, CI 1.03–1.18)

Global Rating

Table 2: Breast Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Cohort Studies						
Dolapsakis 2001	Cohort study of 1062 women in Crete who had a mammogram for the first time between 1988-1993; all women re-evaluated every 1 or 2 yrs until 1998; 2 groups - exposed (522) who had at least 10 yrs work in greenhouses, and non-exposed (540), who had non-agricultural occupations.	Mixed occupational exposure, but pesticides associated with agriculture (mainly organophosphates and organocarbamates); exposed women had worked for 10 yrs or more on a farm for at least 4 hrs/day.	age, family history of breast cancer, age at menopause and menarche, parity, contraceptive and estrogen use.	detection rates expressed as proportions, chi square; some RR's	Exposed women had a significantly higher risk ($p < 0.05$) than non-exposed for fibroadenoma (RR 4.86, CI 1.4–16.7), ductal hyperplasia (RR 1.87, CI 1.1–3.13), sclerotic adenosis (RR 1.88, CI 1.1–3.1), fibrohyperplastic disease (RR 1.85, CI 1.3–2.6), cystic disease (RR 1.44, CI 1.1–2.0) and inflammatory mastitis (RR 2.21, CI 1.2–4.0) in mammographic findings. There were no significant differences in malignant changes.	5,5
Case-Control Studies						
Band 2000	Case control study of 1018 women with incident breast cancer compared to 1020 population controls in BC; all under the age of 75 yrs and dx between 1988–1989.	Mixed pesticide exposure assessed through questionnaires about occupation; jobs coded and classified according to exposure; 'ever'/'never' categories for being in a given occupation.	smoking, alcohol consumption, ethnicity, marital status, education, age at menarche, age at menopause, family history of breast cancer, BMI, use of birth control pills, HRT, reproductive history, breast feeding, history of breast biopsy	OR, logistic regression	Increased risk of breast cancer for pre-and post-menopausal group combined for occupation with fruit and other vegetable farms (OR 3.11, CI 1.24-7.81); fruit farms only (OR 2.94, CI 0.90-9.60), and other vegetable farms (OR 7.33, CI 1.16-46.2).	5,4
Duell 2000	Case control study in North Carolina; 862 cases with breast cancer	Pesticides classified as insecticides, herbicides, and fungicides;	age at dx, age at menarche, parity, age at first birth, smoking	OR, unconditional logistic regression	Increasing duration of farming was inversely associated with breast cancer risk; Also	5,6

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
	diagnosed between 1993–1996; 790 controls	exposure assessed through a questionnaire administered within 4 months of diagnosis; detailed questions on farm-specific exposures; categorized as never, 1–16 yrs, or >16 yrs exposed.	history, alcohol, education, history of lactation, oral contraceptive use, family history of breast cancer, BMI, duration of washing laundry for pesticide users, benign breast biopsy, HRT, menopausal status.		increased risk associated with being present in fields during or shortly after pesticide application (OR 1.8, CI 1.1–2.8) and for those reported not using protective clothing while applying pesticides (OR 2.0, CI 1.0–4.3)	

Ecological Studies

Abdalla 2003	Ecological study; used breast cancer mortality data from the National Cancer Institute website and looked at the entire population of Mississippi; considered mortality in different regions of the state which have different pesticide use rates.	Mixed pesticide exposure; Proxy for pesticide exposure - total # of acres planted during 1997-2000 for each Statistical Economic Area and by type of crop.	Age, race	SMR, Spearman correlation coefficient	In some areas of heavy pesticide use the rate of breast cancer was elevated; strongest correlation between white women and rice crops planted in one region ($\rho=0.674$, $p<0.03$).	4,4
Hopenhayn-Rich 2002	Ecological study; used the Kentucky cancer registry for information about breast cancer incidence and compared to exposure indices to atrazine; included population of Kentucky (3 mill)	Atrazine; exposure index developed based on public water measurements, acres of corn planted, and pounds of atrazine sold.	age, county, race, education, degree of urbanisation, ses, use of public water	RR, Poisson	The breast cancer effect estimates indicate a null association with increasing exposure to atrazine.	5,6
Kettles 1997	Ecological study; used the Kentucky cancer registry for information about breast cancer incidence and compared to exposure indices for triazine	Triazine herbicides; exposure index developed based on water contamination data, corn crop production, and	age, race, age at first live birth, income, level of education, county	OR, Poisson	An increase in breast cancer risk with medium and high levels of triazine exposure (OR 1.14, $p<0.0001$ and OR 1.2, $p<0.0001$); for low exposure OR	5,6

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
	herbicides; included population of Kentucky.	pesticide use data (from a 1979 survey); counted then classified into low, medium, or high exposure levels.			1.0.	

Table 3 Kidney Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Cohort Studies						
Fear 1998	Retrospective cohort; 167, 703 childhood deaths in Wales and England during 1959-1963, 1970-1978, and 1979-1990; looked at cause of mortality for these children.	Agricultural and/or horticultural pesticides; exposure to these determined by paternal occupation as a farmer, agricultural workers, agricultural machine driver, gardener, and forester; exposure assumed if father had one of these jobs.	age, year of death, paternal social class	PMR, Poisson	There was a statistically significant increase in death from kidney cancer in those children with paternal occupational exposure to pesticides (PMR 1.59, CI 1.18–2.15)	4,4
Ramlow 1996	Retrospective cohort study of 770 employees of the Dow Chemical Company in Michigan.	Exposure to PCP assessed by job description, wipe samples, area exposure monitoring, personal breathing zone data, duration of exposure - this gave a cumulative exposure category between 1-3; exposure assessed for the period 1940–1989.	age, period of employment, general employment status (hourly vs salaried)	SMR, Mantel-Hanzel	There were no elevated levels of any cancer that was significant; when cumulative exposure was considered, kidney cancer was significantly elevated (SMR 502, CI 101–1468)	4,4
Case-Control Studies						
Buzio 2002	Case control study in Italy; 100 renal cell cancer cases and 200 controls.	Mixed pesticide exposure assessed by an interview; subjects asked questions about occupation and then an industrial hygienists coded according to level of exposure: labelled short or	age, smoking habits, gender, use of drugs, BMI, use of well water	OR, logistic multiple regression	Renal cell cancer was increased with prolonged pesticide exposure (OR 2.0, CI 0.8–4.7); for short exposure (OR 1.1, CI 0.2–5.9); these were the only ORs for pesticides provided.	4,4

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Hu 2002	Case control study in eight Canadian provinces; 1279 cases included subjects with kidney cancer from provincial cancer registries; 5370 population controls.	long exposure (greater or less than 10 yrs). Mixed pesticide exposure; assessed by a questionnaire; detailed questions about occupation and exposure to benzene, herbicides, pesticides, and other variables.	age, sex, province, ses, smoking habits, diet, BMI, physical activity, use of vitamins, alcohol	OR, logistic regression	Exposure to pesticides associated with increased risk of kidney cancer (OR 1.8, CI 1.4–2.3); higher OR if males exposed to herbicides in a dose response relationship (greater than 16 yrs exposure OR 2.0, CI 1.4–2.7); for women (OR 1.3, CI 0.9–1.8).	5,5
Mellemgaard 1994	Case control study in Denmark; 365 cases identified by cancer registry, between the ages of 20-79, born and living in Denmark; 396 controls	Insecticides and herbicides; exposure assessed with interviews w/questions about occupation and exposure; occ coded based on exposure, but occupation must have lasted at least one yr, and occurred at least 10 yrs prior to interview.	gender, age, smoking habits, BMI, ses	OR, logistic regression	Increased risk for RCC in men with over 20 yrs exposure to insecticides and herbicides (OR 3.9, CI 1.0–15); less than 20 yrs (OR 1.3, CI 0.4–4.1).	4,4
Sharpe 1995	Case control study in Brazil; 109 cases and 218 controls; hospital-based, multicentre; looked specifically at Wilms' tumour.	Mixed pesticide exposure assessed by questions about parents occupation, and agriculture practices of family; interview; for relevant occupations must have been employed at least 6 mos.	income, parental education, age, sex	OR, conditional logistic regression	Consistently elevated risks were seen for farm work involving frequent use of pesticides by both the father (OR 3.24, CI 1.2–9.0) and the mother (OR 128.6, CI 6.4–2569).	4, 4

Table 4 Lung Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Cohort Studies						
Figa-Talamanca 1993	Retrospective cohort study of a group of 2310 male farm workers (over age 15 yrs) who were licensed to handle pesticides in Italy; included those issued pesticides licenses between 1973–1979.	Mixed pesticide exposure; mostly assessed through license information – a small group filled out a questionnaire (but did not have information on quantity or type of pesticide – just use or not).	age	SMR, Poisson	The cohort experienced statistically significant lower mortality for lung cancer (SMR 57, CI 35.6–80.0); this was confirmed in the two age groups considered where the SMR for ages 15–64 was 32 and that for ages 65 and over was 89.	4,4
Kross 1996	Retrospective cohort study of a group of 686 deceased white male members of the Golf Superintendents Association of America; compared to white male US population; included subjects from across the US	Mixed pesticide exposure; could not provide specific exposure information as data source was death certificates; exposure assumed through membership in association.	None	PMR	The cohort experienced higher mortality for all cancers (PMR 136, CI 121, 152), PMR lung cancer 117 (CI 93, 148), PMR brain 234 (CI 121, 454), PMR NHL 237 (CI 137, 410), PMR prostate 293 (CI 187, 460).	4,4
Case-Control Studies						
Brownson 1993	Case-control study to determine occupational risk factors for lung cancer and women; Missouri; 429 cases (294 nonsmokers, 135 ex-smokers), 1021 controls; 1986-1991; actually part of a larger study with a different study question.	Mixed pesticide exposure; assessed through a questionnaire and personal interview regarding questions about occupational exposure.	smoking habits, age, diet, history of previous lung disease	OR, logistic regression	Increased risk of lung cancer in exposed group for all subjects (OR 2.4, CI 1.1–5.6) and lifetime nonsmokers (OR 3.1, CI 1.3–7.5); the risk at 17.5 years or less was an OR of 1.5 (CI 0.4–6.5) and for more than 17.5 years OR 2.4 (CI 0.8–7.0).	5,4

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Pesatori 1994	Nested case control study (retrospective) from cohort of 4411 individuals from 1965-66 licensing applications submitted by pest control firms in Florida; 65 lung cancer cases, 122 deceased controls, 172 living controls; pest control workers.	Mixed pesticide exposure questionnaire with questions about occupation, work practices, and specific chemicals used; completed by next-of-kin as cases were deceased.	age, smoking, diet, other occupations	OR, logistic regression	Statistically significant increased risk of lung cancer for use of carbamates (OR 16.3, CI 2.2-122.5) when cases compared to dead controls, phenoxyacetic acids (OR 22.4, CI 1.8-122.5) when compared to living controls; overall range of OR's between 0.5-22.4.	4,4

Table 5 Ovarian Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Ecological Studies						
Hopenhayn-Rich 2002	Ecological study; used the Kentucky cancer registry for information about ovarian cancer incidence and compared to exposure indices to atrazine; included population of Kentucky (3 mill)	Atrazine; exposure index developed based on public water measurements, acres of corn planted, and pounds of atrazine sold.	Age, county, race, education, degree of urbanization, ses, use of public water	RR, Poisson	For ovarian cancer, the data suggests an inverse association with increasing exposure linked to decreasing incidence rates.	5,6

Table 6 Pancreatic Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Cantor 1999	Retrospective cohort study to compare the causes of death of aerial pesticide applicators and flight instructors; 9961 pesticide applicators and 9969 control flight instructors; US; all men	Mixed pesticide exposure; an index for exposure was estimated based on the number of flight hours.	age	RR, SMR, chi-square	Rates of pancreatic cancer were elevated in the applicator group compared to the instructor group (RR 2.71, CI 1.4–5.3); other RR's were all for other cancers and causes of mortality	5,5
Case-Control Studies						
Alguacil 2000	Case control study for cases of pancreatic cancer diagnosed in one of 5 hospitals in Spain; 164 cases and 238 controls (controls from hospitals, diagnosed with other cancers, and people with suspect pancreatic cancer).	Mixed pesticide exposure; assessed through a series of interviews with detailed questions about occupation, and specific activities related to pesticide exposure; industrial hygienist evaluated these exposure and coded them as high, low, unknown, or none.	age, gender, hospital, smoking, alcohol use, schooling, coffee, diabetes	OR, unconditional logistic regression	Increased risk of pancreatic cancer in the high intensity category for arsenical pesticides (OR 3.4, CI 0.9–12.0) and 'other pesticides' (OR 3.17, CI 1.1–9.2); other OR's ranged between 1 and 3.57).	5,4
Ji 2001	Case control study; 484 cases aged 30-79 yrs, dx b/t 1986-1989; 2095 population controls; Atlanta, Detroit, New Jersey	Insecticides, fungicides, and herbicides; exposure assessed through an interview; job exposure matrix then used to assign a level of exposure by an industrial hygienist (0–3 scale – none, low, mod/high)	age, race, gender	OR, unconditional logistic regression	Excess risks for pancreatic cancer for occupational exposure to fungicides (OR 1.5, CI 0.3–7.6) and herbicides (OR 1.6, CI 0.7–3.4); an increased risk for insecticide exposure disappeared after adjustment for fungicide and herbicide exposure.	5,4

Table 7 Prostate Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
Cohort Studies						
Alavanja 2003	Prospective cohort study of 55,332 male pesticide applicators; commercial and farmer applicators in Iowa, and private applicators in North Carolina; those with a previous history of prostate cancer were excluded; recruited from a pesticide certification testing session.	45 common agricultural pesticides; questionnaire at enrollment; some pesticides asked 'ever'/'never' use, others asked for more detailed info about duration of use and frequency; info also collected about protective equip use, occurrence of spills, application method.	age, race, state of residence, license type, education, smoking, alcohol use, red meat consumption, vitamin use, fruit and veg intake, BMI, family history of prostate cancer,	SIR, unconditional logistic regression analysis	Increase in prostate cancer in participants compared to the rest of the population (SIR 1.14, CI 1.05–1.24), increase in prostate cancer linearly with the use of methyl bromide (up to OR 3.47, p<0.004); increase in prostate cancer in those with a family history of prostate cancer with use of several insecticides and butylate (OR 2.58).	7,7
Dich 1998	Retrospective cohort study of male pesticide applicators in Sweden (20,025)	Exposure assessment was only done on a subsample of the group (n=268); 92% of them had been exposed for at least one day.	age	SIR by year of birth	Elevated risk of prostate cancer, higher in younger applicators (SIR 1.13 all age groups, SIR 2.03 for younger pesticide applicators)	4,4
Fleming 1999	Retrospective cohort study of licensed pesticide applicators in Florida; 33,658 members; 1975-1993; compared to general pop of Florida; mainly men in the cohort, but some women.	Mixed pesticide exposure assessed by pesticide license info; number of yrs of licensure is a proxy for the length of pesticide exposure.	age, calendar time	SIR, Breslow and Day	Among males, prostate cancer and testicular cancer were significantly elevated (SIR 1.91, CI 1.72–2.13 and SIR 2.48, CI 1.57–3.72); this incidence had an SIR 1.98 (CI 1.75–2.24) in 1975-1979, SIR 1.86 (CI 1.44–2.38) in 1980-1984, SIR 1.79 (CI 1.20–2.57) in 1985-1989, and SIR 0.71 (CI 0.14–2.07) in 1990–1994.	6,5
Kross 1996	Retrospective cohort study of a group of 686 deceased white male members of the Golf Superintendents Association of America; compared to white male US population; included	Mixed pesticide exposure; could not provide specific exposure information as data source was death certificates; exposure assumed through	None	PMR	The cohort experienced higher mortality for all cancers (PMR 136, CI 121, 152), PMR lung cancer 117 (CI 93, 148), PMR brain 234 (CI 121, 454), PMR NHL 237 (CI 137, 410), PMR prostate 293 (CI 187,	4,4

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
	subjects from across the US	membership in association.			460).	
MacLennan 2002	Retrospective cohort of 2045 subjects who worked at a plant in Louisiana that made pesticides; subjects had to have worked there for at least 6 mos by the end of 1992, had worked in jobs involving potential contact with triazines or precursor chemicals.	Triazine herbicides; proxy exposure according to area of the plant employed and work history, job description; assessed from work records.	age, race, gender, years worked, years since hire, employee group	SIR, Poisson	There was an increased incidence of prostate cancer in this group: SIR 175 (CI 83–312) in all types of employees, SIR 394 (CI 128–920) in actively working employees, SIR 119 (CI 44–260) in inactively working or contract employees.	5,5

Case-Control Studies

Mills 2003	Nested case control study within a cohort of predominantly Hispanic labor union in California - United Farm Workers of America; 222 cases and 1110 controls	Several pesticide exposures evaluated; assessed by using California's pesticide use reporting system - proxy measurement based on total number of pounds of pesticide active ingredient applied in a given county in a given year.	age, home use of pesticides and other toxins, lifestyle factors such as smoking	OR, Mantel-Hanzel, conditional logistic regression	Prostate cancer risk increased with exposure to several chemicals: dichlorvos, early dx OR 1.2, late dx OR 1.56; heptochlor, early dx OR 1.33, late dx OR 1.4, lindane, early dx OR 1.04, late dx OR 1.85, simazine, early dx OR 1.2, late dx OR 2.16	4,4
Settimi 2003	Case control study in Italy of men with cancer b/t ages 20-75; 124 cases and 659 controls (individ with other type of cancer).	Several pesticide exposures evaluated by a questionnaire; also included 10 crop-specific forms; assigned an exposure of probably exposed or not exposed.	age, family history of prostate cancer, smoking, education, interview (direct vs indirect)	OR, unconditional logistic regression	Increased risks among farmers exposed to organochlorine insecticides and acaricides (OR 2.5, CI 1.4-4.2).	5,5

Ecological Studies

Sharma-Wagner 2000	Ecological study; in Sweden; linked 36,269 prostate cancer cases with employment info from the National Census (1961-1979).	National census database provided info about occupation which was used as a proxy measurement for exposure.	age, occupation	SIR, Poisson	Certain occupations have increased rates of pc, including those with pesticide exposure.	4,4
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Table 8 Stomach Cancer

<u>Reference</u>	<u>Population Description</u>	<u>Pesticides Type and Exposure Assessment</u>	<u>Covariates</u>	<u>Statistical Analysis</u>	<u>Measures of Association and Values</u>	<u>Global Rating</u>
<i>Ecological Studies</i>						
Van Leeuwen 1999	Ecological study; age standardized cancer incidence ratios for 1987–1991 from the Ontario Cancer Registry; compared with levels of contamination of drinking water and related agricultural practices; 40 ecodistricts in Ontario.	Atrazine and nitrate were measured from the drinking and ground water; Ontario Landscape Resource Unit provided information about pesticide use.	alcohol consumption, smoking, education level, income, occupational exposures, age, sex	least squares regression analysis	Atrazine contamination levels were positively associated with stomach cancer incidence (p<0.05), and nitrate was negatively associated with stomach cancer incidence; no other values provided.	5,5