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SUMMARY AND COMMENTS ON THE **PRENATAL ORIGINS OF CANCER SPREADSHEET**

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INTRODUCTION

The Prenatal Origins of Cancer Spreadsheet (formerly the Fetal Origins of Cancer Spreadsheet) presents the results of a comprehensive search of the scientific literature for evidence that postnatal cancers may be determined prior to birth. The spreadsheet contains over 750 published articles examining a wide range of exposures from smoking and air pollution, to toxic chemicals, to maternal factors such as illness and medication. Studies were categorized according to the exposure and the system affected (e.g., blood, brain, breast) and summary tables and charts were created to help describe the data.

To accomplish the above, we conducted numerous searches of the published scientific literature on the prenatal origins of cancer. Computerized database searches of the Web of Science and PubMed were performed using terms such as "in utero or prenatal or fetal origins or gestational and cancer". Abstracts were used to select relevant articles which were read, analyzed, and categorized in an Excel spreadsheet according to two main characteristics: the exposure (for example, pesticides, industrial chemicals, or medications) and the system or endpoint (for example, the blood, the brain, or the liver). This procedure resulted in nearly 600 scientific studies and over 150 review articles and commentaries spanning the years from 1972 to 2007. Although it is our goal, we do not claim to have included every article on the prenatal origins of cancer in our spreadsheet. In particular, the number of studies published on the impact of prenatal nutrition on adult and childhood diseases, stemming largely from the work of D.J. Barker, would be enough for an entire spreadsheet on its own. We did not include these studies as they have been summarized elsewhere[1].

Note that the current version of this product represents several changes from earlier versions. In particular, the spreadsheet data were organized differently in order to make it easier to sort and use. In addition, the title was changed from fetal origins to prenatal origins to more accurately describe the wide range of exposures currently being studied.

One point to keep in mind is that these studies report on exposures that occurred prenatally, that is, from pre-fertilization to birth. Prenatal exposures can have very different endpoints than the same exposure experienced later in life for at least two reasons. One, they represent a route of exposure (through the placenta) that will never be experienced again. Two, the critical life systems of the individual are in a state of construction. This underscores the fact that the developing embryo and fetus experience and react in different ways than a baby, child, adolescent, or adult and that gross generalizations about the consequences of exposure cannot be made based on postnatal data alone.

SUMMARY

The following tables report the number of experimental studies (*in vivo* and *in vitro*) in the spreadsheet by year, study type, and species.

Year of Publication	Number of Studies
1970-79	24
1980-89	65
1990-99	223
2000-07	284

Type of Study	Number of Studies
In vivo	248
Case control	178
Cohort	36
General epidemiological	33
Case study	18
In vitro	64
Follow Up	6
Meta-analysis	5
Prospective	4
Other	5

Species	Number of Studies
Human	335
Mouse	127
Rat	94
Hamster	22
Other/mixed	18

The table below shows the number of positive cancerous findings for each of the eight endpoints most frequently associated with cancers of prenatal origin. Note that this does not include the *in vitro* studies that were categorized differently with regards to the system affected. Those studies are reported on a separate spreadsheet in the Excel file.

Endpoint	No. of positive findings
Brain & Nervous System	111
Leukemias	95
Breast	63
Female Reproductive System (uterus, ovaries, cervix, vagina)	52
Lung & Respiratory System	51
Male Reproductive System (prostate, testes, seminal vesicles)	39
Liver	38
Kidney	28
Lymphomas	26

Analysis by the Type of Prenatal Exposure

Smoking. Of the 44 studies on maternal smoking of tobacco cigarettes, 45% showed evidence of cancer and 27% showed increased risk for cancer. Among the studies showing a link between smoking and cancer (not just risk), the largest number of findings were in the brain and nervous system, followed by leukemias and lymphomas, then lung and respiratory cancers, and finally liver cancer. Compared to studies of cigarette smoking in general, studies of polycyclic aromatic hydrocarbons (PAHs) related to smoking were less likely to be associated with cancer (36%) and more likely to be associated with a risk of cancer (57%).

Air Pollution. Of the 7 studies on PAHs (polycyclic aromatic hydrocarbons) in air pollution, none showed significant associations with cancer, although 6 showed increased risk. This is typically due to the design of the studies, which focused on biomarkers or endpoints that are pre-cancerous. Studies of MC (3-methylcholanthrene) and other pollution related exposures were more likely to be associated with cancer (75% and 85% respectively). The highest risks, according to the systems studied, were for leukemias and lymphomas, followed by liver cancer, and lung and respiratory cancers.

Pesticides (insecticides, herbicides, and fungicides). Eighty-six percent of the studies on pesticides showed a significant association with cancer. By far, the two most common cancerous endpoints were the brain and nervous system and leukemias and lymphomas. These were followed by cancers of the kidney, breast, and lung and respiratory systems.

Radiation. Seventy percent of the studies on radiation found evidence of cancer. Both ionizing and non-ionizing radiation were most often associated with leukemias and lymphomas. Ionizing radiation was also frequently associated with cancers of the male reproductive system, the lung and respiratory systems, and the liver.

Industrial Chemicals and Fuels. Of the 50 studies on industrial chemicals, 70% found at least one association with cancer. The highest number of positive findings for this exposure risk was in leukemias and lymphomas, followed closely by brain and nervous system cancers. Female reproductive and breast cancers were also frequently associated with exposure to industrial chemicals. The liver and the lung and respiratory systems were the next two most affected sites. All four studies of fuels showed a significant link to cancer, mostly of the brain and nervous system.

Metals. Seventy percent of the studies on prenatal exposure to metals (mostly arsenic and lead) showed significant associations with cancer. The highest categories were leukemias and lymphomas, and kidney cancer. The brain and nervous system, liver, male reproductive system, and the eye also had high numbers of positive findings. Finally, several associations were found between exposure to metals and cancers of the lung and respiratory system, and the adrenal system.

Research Chemicals. Research chemicals do not necessarily represent environmental exposures, however, they do provide valuable information on cancer causing agents. As such, they were included in our spreadsheet. Of the 49 studies conducted with research chemicals (all performed

on animals), 92% found associations with cancer. By far, the most commonly studied chemical was ENU (ethylnitrosourea), with 29 studies, 18 of which found cancer in the brain and nervous system. Among the other research chemicals exposures, the highest category of findings was in the lung and respiratory system. Substantially less frequent were findings in the kidney, liver, and male reproductive systems.

Food and Water. Sixty nine percent of the studies of food and water exposures were related to cancer. The single most-studied exposure was N-nitroso compounds (typically found in cured meats), which were most frequently associated with cancers of the brain and nervous system. Other food and water exposures were frequently linked to breast cancer.

Medication. Of the 97 studies of medication related exposures, 50 were on DES (diethylstilbestrol), which was most frequently associated with female and male reproductive cancers and breast cancer. The next highest exposure categories were leukemias and lymphomas and the brain and nervous system, followed by the lung and respiratory system.

Alcohol and Recreational Drugs. Of the 13 studies on alcohol and drug exposures, 62% were related to cancer. The two highest categories, with three studies each, were the brain and nervous system and leukemias and lymphomas.

Genetic. Nineteen studies were performed on genetic and chromosomal factors. Of these, 84% found evidence of cancer, primarily leukemias and lymphomas. The next highest category was the digestive system.

Maternal and Birth Factors. This category is comprised of maternal illness, hormones, birth weight and general factors such as maternal age. Across all four categories, the systems most affected were the breast, leukemias and lymphomas, the brain and nervous system, and the male reproductive system. The other systems were far less commonly studied. Note that these studies, particularly those listed as "general" were difficult to categorize as they were often large retrospective studies with many potential factors associated with the cancer of interest.

COMMENTS

When we began researching this topic we had little to guide us. As far as we knew, no one had used the umbrella topic of "fetal origins of cancer" to amass the scientific research on such varied environmental exposures as air pollution, metals and medication. We now have a database of nearly 600 experimental studies and over 150 reviews and commentaries. Our goal is to make the scientific literature on the prenatal origins of cancer available in an easy-to-use format for researchers, activists and others to use as they see fit.

For many years it was believed that childhood cancers were caused by genetic and chromosomal changes to the fetus. Our analysis demonstrates that environmental exposures such as pesticides and industrial chemicals are also important to consider. Understanding the interaction of genes and the environment, including epigenetic processes, holds the key to our comprehension of what predisposes a person to getting cancer later in life. This is clearly one of the most important paths for cancer research.

Equally important is the complex relationship among the exposures we termed "maternal and birth factors". Many variables such as maternal age, pregnancy hormones, maternal illness and birth weight have been found to predict cancer. Some are likely to be root causes, while others, such as birth weight, may be both symptoms and causes. It has been hypothesized that what connects these variables is disruption of the endocrine system. Understanding the hormonal fluctuations (natural and externally induced) that occur from fertilization to birth is critical to our comprehension of the prenatal origins of cancer, as well as many other diseases faced by children and adults in the modern world.

Although much of this news is grim, we do have examples in which human exposure to carcinogens has been greatly reduced due to research combined with intense public scrutiny and action. One such example is exposure to cigarette smoke, first-hand, second-hand and *in utero*. The numerous bans on smoking in public places, Surgeon General's warnings, and public education about the carcinogenic effects of cigarettes, particularly for pregnant women, are all changes that were produced by the dedicated efforts of scientists, activists and the legal community. Another example is DES, a drug that was commonly prescribed between 1938 and 1971 for complications of pregnancy. The risk of DES to the fetus was made a national issue by a strong coalition of DES mothers and daughters. Their efforts, backed by scientific research, led to the 1971 FDA advisement that physicians stop prescribing DES to pregnant women. The DES story stands out as a unique example of action taken to reduce exposure based specifically on cancer produced in an offspring.

Over the last century, millions of individuals have experienced these exposures *in utero* and little has been done to reduce the threat to future generations. This compilation of research makes it clear that we can no longer ignore the growing body of literature linking prenatal exposure with various cancers, particularly those of the brain and nervous system, and leukemias and lymphomas. By supporting the science behind the action, our hope is that every child will begin life with the cleanest slate possible and the best hope for the future.

[1] Boo, H. A. and Harding, J. E. The developmental origins of adult disease (Barker) hypothesis. Australian & New Zealand Journal of Obstetrics & Gynaecology. 2006; 46:4-14.