Oral contraceptive use is associated with prostate cancer: An Ecologic Study

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Oral contraceptive use is associated with prostate cancer: An Ecologic Study

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Key Words: oral contraceptives, prostate cancer, ecologic study

Abstract

Introduction- Recently there have been several studies suggesting that estrogen exposure may increase the risk of prostate cancer (PCa). In this report we examine associations between PCa incidence and mortality and population-based use of oral contraceptives (OC's). We hypothesized that OC`s by-products may cause an environmental contamination leading to an increased low level estrogen exposure and therefore higher PCa incidence and mortality.

Methods- the hypothesis was studied in an ecologic study. We used data from the "international agency for research on cancer" (IACR) to retrieve age-standardized rates of prostate cancer in 2007 and the "United Nations 2007 use of contraceptive report" to retrieve data on contraceptive use. We subsequently used a Pearson correlation to associate the percentage of women using OC`s , intrauterine devices, condoms or vaginal barriers to the age standardized prostate cancer incidence and mortality. We performed these analyses by individual nation and by continent worldwide.

Results- OC`s use was significantly associated with prostate cancer incidence and mortality in the individual nation world wide ($r=0.63$ and $r= 0.51$, respectively $p<0.05$ for all). PCa incidence was also associated with OC`s use in Europe ($r=0.545$ $p<0.05$) and by continent ($r= 0.522$ $p<0.05$). All other forms of contraceptives (i.e. intra-uterine devices, condoms or vaginal barriers) were not correlated with prostate cancer incidence or mortality.

Conclusion- In this hypothesis generating ecologic study we have demonstrated a significant association between OC`s and PCa. We hypothesize that oral contraceptive

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effect may be mediated through environmental estrogen levels; this novel concept is worth further investigation.

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Article summary

Article focus:

- Recently there have been several studies suggesting that estrogen exposure may increase the risk of prostate cancer.
- In this report we examine associations between prostate cancer (PCa) incidence and mortality and population-based use of oral contraceptives (OC's).
- We hypothesized that OC`s by-products may cause an environmental contamination leading to an increased low level estrogen exposure and therefore higher PCa incidence and mortality.

Key Message:

- In this hypothesis generating ecologic study we have demonstrated a significant association between female use of oral contraceptive use and prostate cancer.

Strengths and limitations of this study:

- This study is an ecological study and thus has significant limitations with respect to causal inference .It must be considered hypothesis generating, and thought provoking
- This novel concept is worth further investigation.

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Introduction

Prostate cancer (PCa) is the most common male malignancy in the western world and risk factors associated with this cancer remain ill defined (1). The only acknowledged risk factors thus far are: age, ethnicity and family history (1). Several studies have suggested that estrogen exposure may increase the risk of prostate cancer (2-4).

The use of oral contraceptives has exploded over the past 40 years and has had a patchy uptake in terms of global utilization. Emerging literature suggests that oral contraceptive (OC) use may be associated with a variety of medical conditions among consumers such as atheroembolic and even breast cancer (5-8). Aside from disease risk among actual drug consumers, there is also increasing concern about environmental contamination by endocrine disruptive compounds (EDC's) and their association with diseases of increasing incidence such as breast cancer (men and women), early onset puberty, and testicular cancer. EDC's include a variety of compounds used in commercial applications such as detergents, manufacturing, pesticides, cosmetics, and building materials (9). It is plausible that by-products of OC metabolism could be passed via urine into the environment in general or drinking water thus exposing the population at large.

In this report we examine associations between prostate cancer incidence and mortality and population-based use of OC's. In addition, to explore the specific effect of OC, we also examined these outcomes in association with other modes of contraception.

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Methods-

Study Design & Data Sources:

This study utilized a geographic or ecologic design to identify associations between aggregate use of contraception and rates of prostate cancer. We utilized data from the "international agency for research on cancer" (IACR) to retrieve age-standardized rates of country-specific prostate cancer incidence and mortality in 2008 (10). The incidence data in IACR are derived from population-based cancer registries.

The "United Nations 2007 use of contraceptive report" (11) was used to retrieve data on contraceptive use. In this report, data were obtained from surveys of nationally representative samples of women of reproductive age. The estimates for each nation represent weighted averages derived for each country by the estimated number of women aged 15 to 49 in 2007 who are married or in union. These estimates are based on data on the proportion of women married or in union in each country contained in World Marriage Database 2006 (12) and on estimates of the number of women by age group obtained from World Population Prospects: The 2006 Revision (13).

The following information was collected: percent of woman in reproductive age using oral contraceptives, intrauterine devices, condoms or vaginal barriers. The rationale for examining alternate uses of birth control was to examine for specificity for the OC as it is plausible that this measure is a marker of sexual activity, which itself, has demonstrated some inconsistent association with prostate cancer (14). In addition to global incidence and mortality, we also examined continent specific and Europe specific

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outcomes as we strived to test this association among a more homogenous group with narrower ranges of both OC use as well as prostate cancer incidence/mortality.

Statistical analysis

Pearson correlation was used to associate age-adjusted prostate cancer incidence and mortality rates to the percentage of women using oral contraceptives, intrauterine devices, condoms or vaginal barriers. We performed these analyses by individual nation and by continent worldwide. We randomly identified 60 different nations for the survey ensuring to sample each continent. Probability values less than 0.05 were deemed significant.

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Results-

As shown in Figure 1 (A,B and C) oral contraceptive use was significantly correlated with prostate cancer incidence in the individual nation world wide (fig 1A r=0.63 $p<0.05$) and in Europe (fig1B r=0.545 $p<0.05$) and by continent (Fig1C r= 0.522 $p<0.05$). All other forms of contraceptives (i.e. intra-uterine devices, condoms or vaginal barriers) were not correlated with prostate cancer incidence.

Mortality correlated with oral contraceptive use in the individual nations world wide (Fig 2-A r= 0.51 $p<0.05$). However no correlation was found in prostate cancer mortality rates within Europe or by continent. In addition we did not demonstrate any correlation between other modes of contraceptives and prostate mortality rates.

Table 1 depicts data on contraceptive use and PC outcomes in ten countries with the highest and lowest percentage of OC use. As shown all top 5 OC use nations are European and the lowest percentage are distributed between Asia and Africa.

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Discussion

In this study we have demonstrated a strong correlation between the country-specific female oral contraceptive use and incidence of prostate cancer among world wide, continent and even intra-European nations. This correlation appeared specific to OC as no association was demonstrated with other forms of contraception such as intrauterine devices, condoms or vaginal barriers. Furthermore, prostate cancer mortality was also associated with OC use when examined globally.

This study represents the first systematic analysis of associations between OC use and prostate cancer. This study is an ecological study and thus has, as all correlational studies, significant limitations with respect to causal inference (15).As such; it must be considered hypothesis generating.

There are several plausible explanations for this association. Prostate cancer has been associated with sexual transmission. Although, no particular infectious agent has been identified, recent interest in the Xenotropic murine leukemia virus-related virus (XMRV) and its discovery in semen has raised this as a possible candidate (14,16). Clearly more studies are needed. We would hypothesize however; that if sexual activity were the explanation for the above observations, similar outcomes would be noted for other forms of contraception and that one could even assume a protective effect. As we do not have individual level data, these hypotheses are not testable and would require a long latency period.

Another plausible explanation for the association between OC use and prostate cancer is the potential environmental impact of OC's. The last two decades have witnessed growing scientific concerns and public debate over the potential adverse

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effects that may result from exposure to a group of chemicals that have the potential to alter the normal functioning of the endocrine system in wildlife and humans. These chemicals are typically known as endocrine disturbing compounds (EDCs). Temporal increases in the incidence of certain cancers (breast, endometrial, thyroid, testis and prostate) in hormonally sensitive tissues in many parts of the industrialized world are often cited as evidence that widespread exposure of the general population to EDCs has had adverse impacts on human health. Oral contraceptives in use today can potentially act as EDC's as they frequently contain high- doses of ethinylestradiol, which is excreted in urine without degradation. These can then end up either in the drinking water supply or passed up the food chain (9). Oral contraceptives were made publicly available in the 1960s, and are widely used since the 1980s hence the exposure to these substances even in small quantities may be chronic enough (20-30 years) to have a clinically significant effect.

There are limited epidemiologic data that have examined associations between prostate cancer and exposure to environmental EDCs . These are largely derived from occupational exposures, and many lack internal exposure information. In one retrospective cohort epidemiology study of Canadian farmers linked to the Canadian National Mortality Database, a weak but statistically significant association between acres sprayed with herbicides and prostate cancer deaths was found (17). Multigner et al (18), have recently demonstrated that environmental exposure to chlordecone, an organochlorine insecticide with well defined estrogenic properties, increase the risk of prostate cancer. Studies on workers in Germany (19) and the USA (20), showed a small but statistically significant excess in prostate cancer mortality, based on a limited number

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of cases. Other studies have failed to demonstrate this association (21-23). All former studies looked at occupation exposure to high concentrations in pesticides however in our study we speculate that low concentrations in drinking water supply may cause PCa, due to the more chronic everyday exposure.

Some may argue that our results only reflect screening and treatment patterns for prostate cancer with the more developed countries having both a higher use of oral contraceptives and a higher incidence of prostate cancer. For this reason we analyzed 25 well developed European countries separately and demonstrated similar incidence trends. Furthermore, the mortality data should be free of diagnostic bias.

In conclusion, we have demonstrated a significant correlation between oral contraceptive use and prostate cancer incidence and mortality. Classic case control and cohort studies may not reveal this association as we are hypothesizing an environmental effect. Tissue correlation and environmental studies are encouraged.

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Legends to figures-

Figure 1- Correlation between PCa incidence expressed as age standardized per 100,000 persons and percent of contraceptive use in women aged 15-49 in individual nation world wide (fig 1A) and in Europe (fig1B) and by continent (Fig1C).

Figure 2- Correlation between PCa mortality expressed as age standardized per 100,000 persons and percent of contraceptive use in women aged 15-49 in individual nation world wide (fig 1A) and in Europe (fig1B) and by continent (Fig1C).

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Table 1- Contraceptive use and PC outcomes in ten countries with the highest and lowest percentage of OC use.

		OC use	PCa incidence	PCa mortality
Top 5 OC users	**Germany**	52.6	113	21.2
	Netherland	49	98.4	26
	Belguim	46.7	160.8	36.9
	Purtugal	45.3	101.2	24.7
	France	43.8	133.5	23.8
Lower 5 OC users	**Pakistan**	1.9	5.2	4
	Nigeria	1.8	22.7	18.6
	China	1.5	4.3	1.8
	Japan	1.1	22.7	5
	Chad	0.5	20.4	11.6

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Figure 1-A

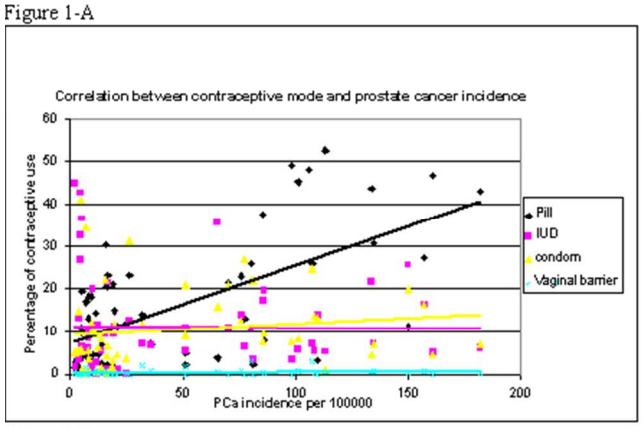

Figure 1-B

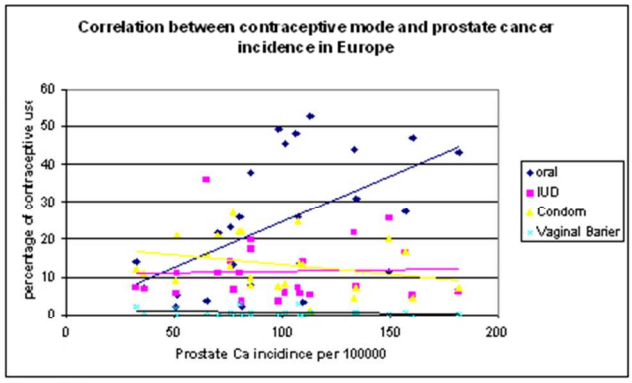

Figure 1-C

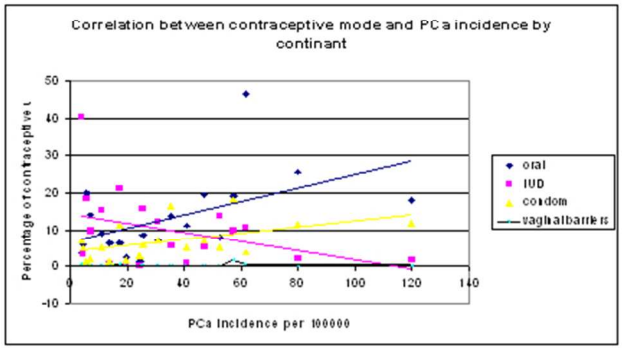

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Figure 2-A

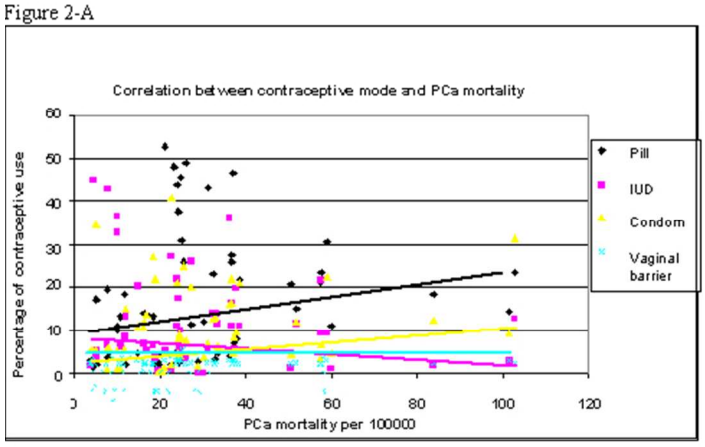


Figure 2-B

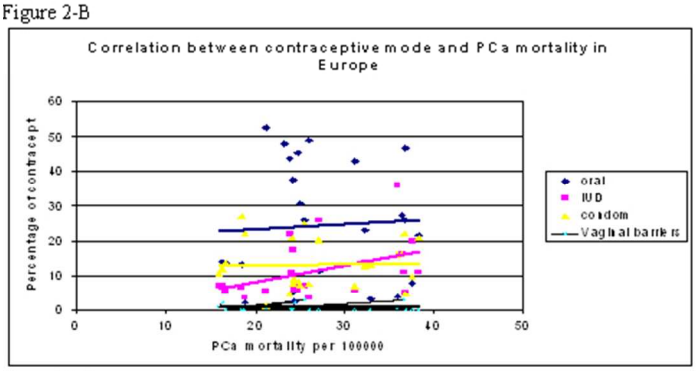
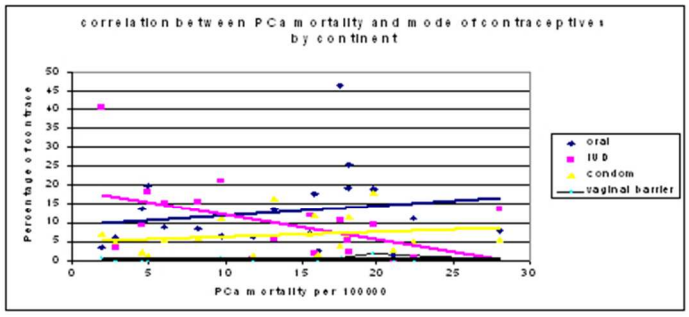


Figure 2-C



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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not relevant

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not relevant
		(b) Give reasons for non-participation at each stage	Not Relevant
		(c) Consider use of a flow diagram	Not Relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not Relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not Relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not Relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Relevant
		Cross-sectional study—Report numbers of outcome events or summary measures	Not Relevant
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not Relevant
		(*b*) Report category boundaries when continuous variables were categorized	Not Relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not Relevant
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Abstract

Introduction- Recently there have been several studies suggesting that estrogen exposure may increase the risk of prostate cancer (PCa). In this report we examine associations between PCa incidence and mortality and population-based use of oral contraceptives (OC's). We hypothesized that OC`s by-products may cause an environmental contamination leading to an increased low level estrogen exposure and therefore higher PCa incidence and mortality.

Methods- the hypothesis was studied in an ecologic study. We used data from the "international agency for research on cancer" (IACR) to retrieve age-standardized rates of prostate cancer in 2007 and the "United Nations 2007 use of contraceptive report" to retrieve data on contraceptive use. We subsequently used a Pearson correlation and a multivariable linear regression to associate the percentage of women using OC`s , intrauterine devices, condoms or vaginal barriers to the age standardized prostate cancer incidence and mortality. We performed these analyses by individual nation and by continent worldwide.

Results- OC`s use was significantly associated with prostate cancer incidence and mortality in the individual nation world wide (r=0,61 and r= 0,53, respectively p<0.05 for all). PCa incidence was also associated with OC`s use in Europe (r=0.545 p<0.05) and by continent (r= 0.522 p<0.05). All other forms of contraceptives (i.e. intra-uterine devices, condoms or vaginal barriers) were not correlated with prostate cancer incidence or mortality. On multivariable analysis the correlation with OC was independent of nation's wealth.

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Conclusion- In this hypothesis generating ecologic study we have demonstrated a significant association between OC`s and PCa. We hypothesize that oral contraceptive effect may be mediated through environmental estrogen levels; this novel concept is worth further investigation.

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Article summary

Article focus:

- Recently there have been several studies suggesting that estrogen exposure may increase the risk of prostate cancer.
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Strengths and limitations of this study:

- This study is an ecological study and thus has significant limitations with respect to causal inference .It must be considered hypothesis generating, and thought provoking
- This novel concept is worth further investigation.

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Introduction

Prostate cancer (PCa) is the most common male malignancy in the western world and risk factors associated with this cancer remain ill defined (1). The only acknowledged risk factors thus far are: age, ethnicity and family history (1). Several studies have suggested that estrogen exposure may increase the risk of prostate cancer (2-4). While other studies have not found an association (5,6)

The use of oral contraceptives has exploded over the past 40 years and has had a patchy uptake in terms of global utilization. Emerging literature suggests that oral contraceptive (OC) use may be associated with a variety of medical conditions among consumers such as atheroembolic and even breast cancer (7-10). Aside from disease risk among actual drug consumers, there is also increasing concern about environmental contamination by endocrine disruptive compounds (EDC's) and their association with diseases of increasing incidence such as breast cancer (men and women), early onset puberty, and testicular cancer. EDC's include a variety of compounds used in commercial applications such as detergents, manufacturing, pesticides, cosmetics, and building materials (11). It is plausible that by-products of OC metabolism could be passed via urine into the environment in general or drinking water thus exposing the population at large.

In this report we examine associations between prostate cancer incidence and mortality and population-based use of OC's. In addition, to explore the specific effect of OC, we also examined these outcomes in association with other modes of contraception.

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Methods-

Study Design & Data Sources:

This study utilized a geographic or ecologic design to identify associations between aggregate use of contraception and rates of prostate cancer. We utilized data from the "international agency for research on cancer" (IACR) to retrieve age-standardized rates of country-specific prostate cancer incidence and mortality in 2008 (12). The incidence data in IACR are derived from population-based cancer registries. These mostly cover entire national populations but may cover smaller, sub national areas, and, particularly in developing countries, only major cities. While the quality of information from most of the developing countries might not be of sufficient quality, this information is often the only relatively unbiaised source of information available on the profile of cancer in these countries.

The "United Nations 2007 use of contraceptive report" (13) was used to retrieve data on contraceptive use. In this report, data were obtained from surveys of nationally representative samples of women of reproductive age. The estimates for each nation represent weighted averages derived for each country by the estimated number of women aged 15 to 49 in 2007 who are married or in union. These estimates are based on data on the proportion of women married or in union in each country contained in World Marriage Database 2006 (14) and on estimates of the number of women by age group obtained from World Population Prospects: The 2006 Revision (15). Again information may be less accurate for developing countries however this is the best available information on contraceptive use.

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The following information was collected: percent of woman in reproductive age using oral contraceptives, intrauterine devices, condoms or vaginal barriers. The rationale for examining alternate uses of birth control was to examine for specificity for the OC as it is plausible that this measure is a marker of sexual activity, which itself, has demonstrated some inconsistent association with prostate cancer (16). In addition to global incidence and mortality, we also examined continent specific and Europe specific outcomes as we strived to test this association among a more homogenous group with narrower ranges of both OC use as well as prostate cancer incidence/mortality.

Third we used data from The World Factbook (ISSN 1553-8133; also known as the CIA World Factbook) to retrieve information on Gross domestic product (GDP) per capita in each country (17). GDP refers to the market value of all final goods and services produced in a country in a given period. GDP per capita is often considered an indicator of a country's standard of living. We used this data to control for prostate cancer screening tendencies since countries with a higher GDP are more prone to PCa screening. The World Factbook is prepared by the CIA for the use of U.S. government officials. However, it is frequently used as a resource for academic research papers.

Statistical analysis

Pearson correlation was used to associate age-adjusted prostate cancer incidence and mortality rates to the percentage of women using oral contraceptives, intrauterine devices, condoms or vaginal barriers. We performed these analyses by individual nation and by continent worldwide. We randomly identified 87 different nations for the survey ensuring to sample each continent (List of countries included in the analysis can be found in Appendix 1). We used 50% of countries available from each continent (25 of 50

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Africa; 25 of 50 Asia; 24 of 47 Europe; 11 of 23 America and Australia and Newzeland were also included) We did not use all available countries since we aimed at a equal representation of developed an under developed countries (using the entire sample would have caused over-representation of under-developed countries and may have biased our results)

We performed a linear regression model to assess whether mode of contraceptive use is associated with prostate cancer incidence and mortality variables included in our model were: percent of woman in reproductive age using oral contraceptives, intrauterine devices, condoms or vaginal barriers and GDP per-capita in each nation. Probability values less than 0.05 were deemed significant.

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Both authors contributed to the concept, design and analysis of this study. Both Authors have read and approved the final manuscript. No competing interests have been declared by both authors

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Results-

As shown in Figure 1 (A,B and C) oral contraceptive use was significantly correlated with prostate cancer incidence in the individual nation world wide (fig 1A r=0.61, p<0.05) and in Europe (fig1B r=0.545 p<0.05) and by continent (Fig1C r= 0.522 p<0.05). All other forms of contraceptives (i.e. intra-uterine devices, condoms or vaginal barriers) were not correlated with prostate cancer incidence.

Mortality correlated with oral contraceptive use in the individual nations world wide (Fig 2-A r= 0.53 p<0.05). However no correlation was found in prostate cancer mortality rates within Europe or by continent. In addition we did not demonstrate any correlation between other modes of contraceptives and prostate mortality rates.

Table 1 depicts the multivariable analysis of the association of PCa incidence (A) and mortality (B) with mode of contraceptives controlling for GDP per-capita. As shown both incidence and mortality were associated with oral contraceptive use even after controlling for an indicator of a countries wealth (adjusted estimate 1.06 95%CI 0.58-1.6 and 0.75 95% CI 0.31-1.1, for incidence and mortality respectively, p<0.01 for all)

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Deleted: data on contraceptive use and PC outcomes in ten countries with the highest and lowest percentage of OC use. As shown all top 5 OC use nations are European and the lowest percentage are distributed between Asia and Africa.

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Discussion

In this study we have demonstrated a strong correlation between the country-specific female oral contraceptive use and incidence of prostate cancer among world wide, continent and even intra-European nations. This correlation appeared specific to OC as no association was demonstrated with other forms of contraception such as intrauterine devices, condoms or vaginal barriers. Furthermore, prostate cancer mortality was also associated with OC use when examined globally. The correlation to oral contraceptive use was independent of GDP as a measure of countries wealth, and strongest in Europe.

This study represents the first systematic analysis of associations between OC use and prostate cancer. This study is an ecological study and thus has, as all correlational studies, significant limitations with respect to causal inference (18).As such; it must be considered hypothesis generating.

There are several plausible explanations for this association. Prostate cancer has been associated with sexual transmission. Although, no particular infectious agent has been identified, recent interest in the Xenotropic murine leukemia virus-related virus (XMRV) and its discovery in semen has raised this as a possible candidate (17,19). Clearly more studies are needed. We would hypothesize however; that if sexual activity were the explanation for the above observations, similar outcomes would be noted for other forms of contraception and that one could even assume a protective effect. As we do not have individual level data, these hypotheses are not testable and would require a long latency period.

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Another plausible explanation for the association between OC use and prostate cancer is the potential environmental impact of OC's. The last two decades have witnessed growing scientific concerns and public debate over the potential adverse effects that may result from exposure to a group of chemicals that have the potential to alter the normal functioning of the endocrine system in wildlife and humans. These chemicals are typically known as endocrine disturbing compounds (EDCs). Temporal increases in the incidence of certain cancers (breast, endometrial, thyroid, testis and prostate) in hormonally sensitive tissues in many parts of the industrialized world are often cited as evidence that widespread exposure of the general population to EDCs has had adverse impacts on human health. Oral contraceptives in use today can potentially act as EDC's as they frequently contain high- doses of ethinylestradiol, which is excreted in urine without degradation. These can then end up either in the drinking water supply or passed up the food chain (11). Oral contraceptives were made publicly available in the 1960s, and are widely used since the 1980s hence the exposure to these substances even in small quantities may be chronic enough (20-30 years) to have a clinically significant effect.

There are limited epidemiologic data that have examined associations between prostate cancer and exposure to environmental EDCs. These are largely derived from occupational exposures, and many lack internal exposure information. In one retrospective cohort epidemiology study of Canadian farmers linked to the Canadian National Mortality Database, a weak but statistically significant association between acres sprayed with herbicides and prostate cancer deaths was found (20). Multigner et al (21), have recently demonstrated that environmental exposure to chlordecone, an

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organochlorine insecticide with well defined estrogenic properties, increase the risk of prostate cancer. Studies on workers in Germany (22) and the USA (23), showed a small but statistically significant excess in prostate cancer mortality, based on a limited number of cases. Other studies have failed to demonstrate this association (24-26). All former studies looked at occupation exposure to high concentrations in pesticides however in our study we speculate that low concentrations in drinking water supply may cause PCa, due to the more chronic everyday exposure. Furthermore, environmental EDC may affect the unborn child in the state of organogenesis and cause significant genetic or epigenetic malformations.

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In contrast, recently several studies have demonstrated that PCa may not be related to endogenous androgens. The Endogenous Hormones and Prostate Cancer Collaborative Group analyzing (5) 18 prospective studies of 3886 men with PCa and 6438 control subjects, found no associations between PCa risk and serum concentrations of testosterone, calculated free testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate, androstenedione, androstanediol glucuronide, estradiol, or calculated free estradiol. However this study associated serum hormonal levels. EDCs may increase the risk of PCa by affecting tissue levels or causing genetic or epigenetic changes that may not be found using serum levels. Li Tang et al (6) studied the association between repeat polymorphisms of three key estrogen-related genes (CYP11A1, CYP19A1, UGT1A1) and risk of prostate cancer in the Prostate Cancer Prevention Trial (PCPT), The results indicate that repeat polymorphisms in genes involved in estrogen biosynthesis and metabolism may influence risk of PCa. Further studies are needed to determine the role of EDCs in PCa.

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Some may argue that our results only reflect screening and treatment patterns for prostate cancer with the more developed countries having both a higher use of oral contraceptives and a higher incidence of prostate cancer. Unfortunately data on worldwide screening tendencies or PSA use is unavailable. However we included a multivariable analysis controlling for Gross domestic product (GDP) per capita. GDP refers to the market value of all final goods and services produced in a country in a given period. GDP per capita is often considered an indicator of a country's standard of living. In our multivariable analysis oral contraceptive use was associated with both incidence and mortality even when controlling for GDP. We believe this analysis has strengthened our hypothesis considerably, however additional confounding does exist and should be explored in future studies. Finally we cannot report the true levels of EDCs in the water supply and food chain. We hope such data will be available in the near future.

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In conclusion, we have demonstrated a significant correlation between oral contraceptive use and prostate cancer incidence and mortality. Classic case control and cohort studies may not reveal this association as we are hypothesizing an environmental effect. Tissue correlation and environmental studies are encouraged.

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Table 1- Multivariable linear regression of the association of mode of contraceptives and GDP (a measure of country wealth) with

A- PCa incidence

	Estimate	95% CI	p value
Oral Contraceptive use	1.06	0.58-1.6	<0.001
Intra uterine device	0.01	-0.4-0.4	0.9
Condom use	0.9	-0.1-1.9	0.3
Vaginal barrier	0.07	-4-10	0.5
GDP	0.6	0.1-1.1	0.055

B- PCa mortality

	Estimate	95% CI	p value
Oral Contraceptive use	0.75	0.31-1.1	0.06
Intra uterine device	-0.02	-0.4- 3	0.2
Condom use	0.2	-0.1-0.329	0.3
Vaginal barrier	0.01	-2.1-2	0.9
GDP	0.16	0.04-0.9	0.09

GDP- Gross domestic product (GDP) per capita. GDP refers to the market value of all final goods and services produced in a country in a given period. GDP per capita is often considered an indicator of a country's standard of living

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Legends to figures-

Figure 1- Correlation between PCa incidence expressed as age standardized per 100,000 persons and percent of contraceptive use in women aged 15-49 in individual nation world wide (fig 1A) and in Europe (fig1B) and by continent (Fig1C).

Figure 2- Correlation between PCa mortality expressed as age standardized per 100,000 persons and percent of contraceptive use in women aged 15-49 in individual nation world wide (fig 1A) and in Europe (fig1B) and by continent (Fig1C).

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Figure 1A

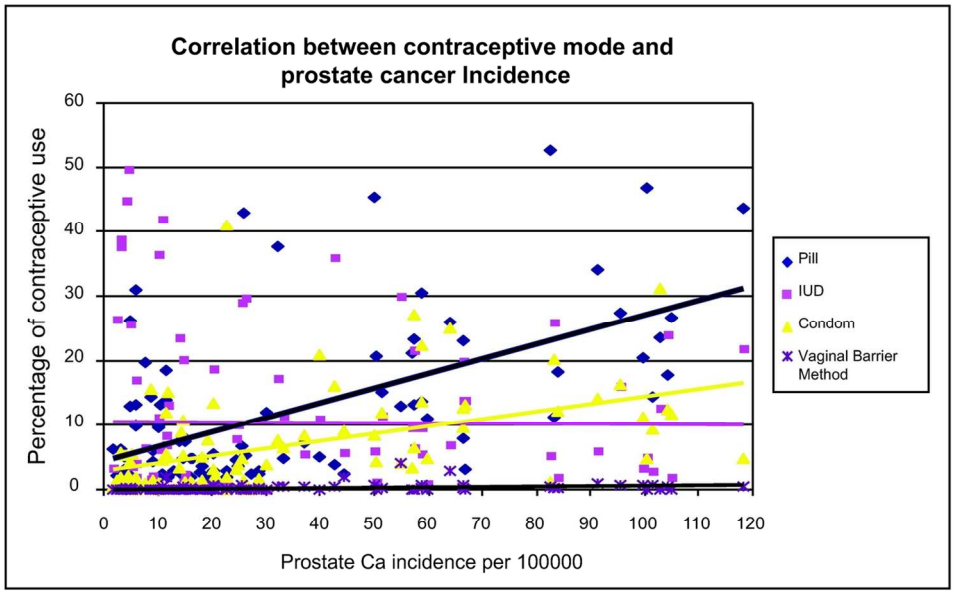

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Figure 1B

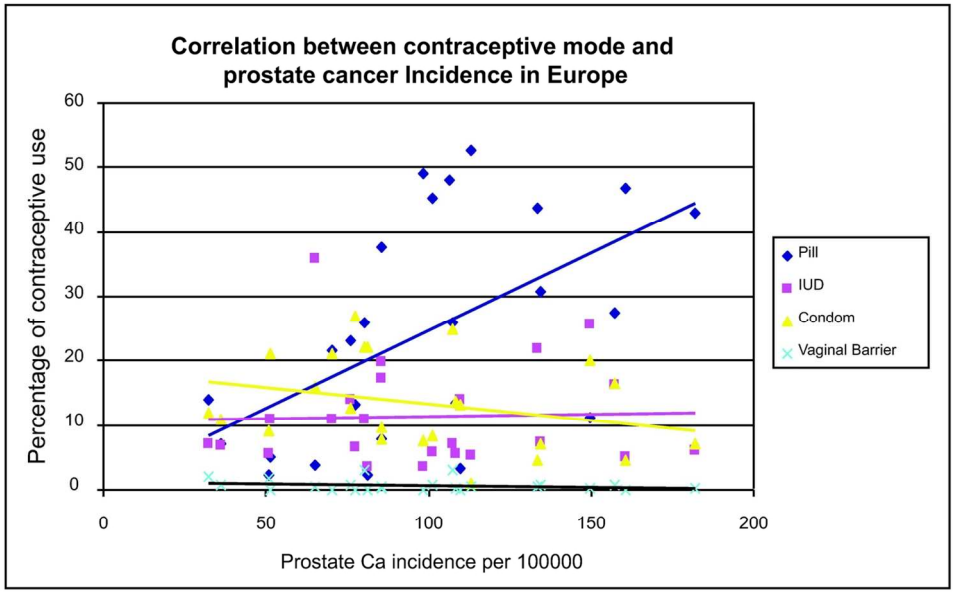

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Figure 1C

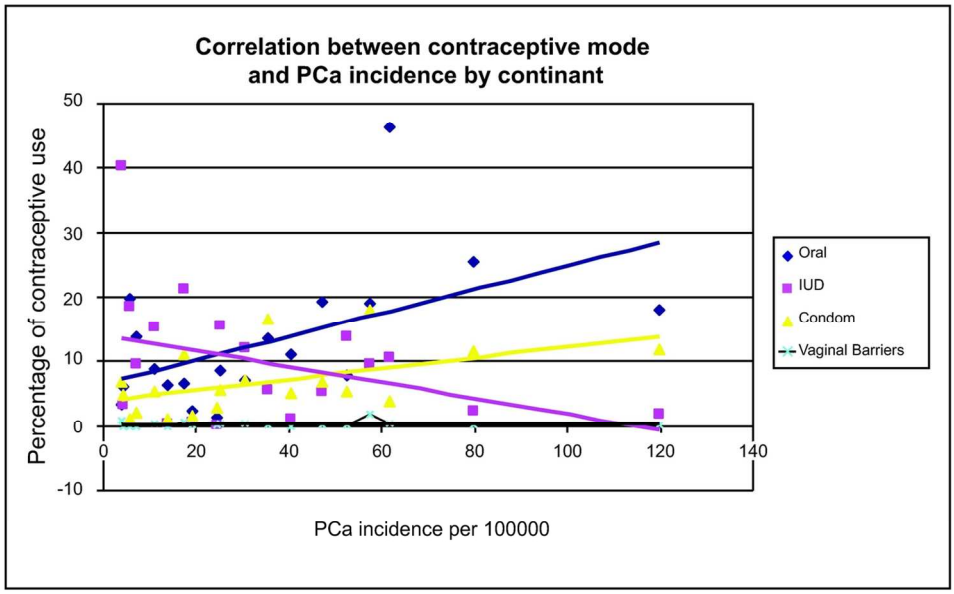

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Figure 2A

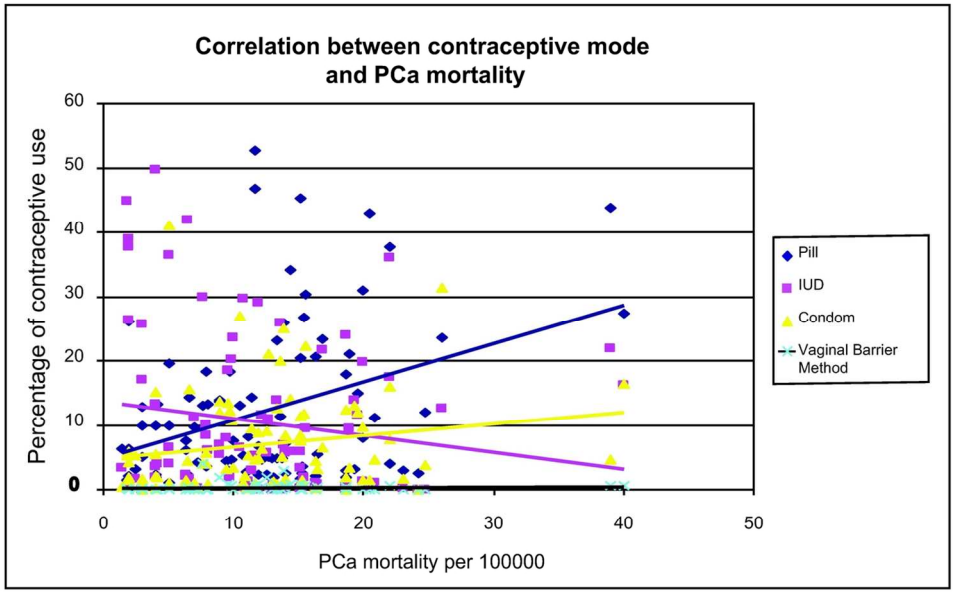

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Figure 2B

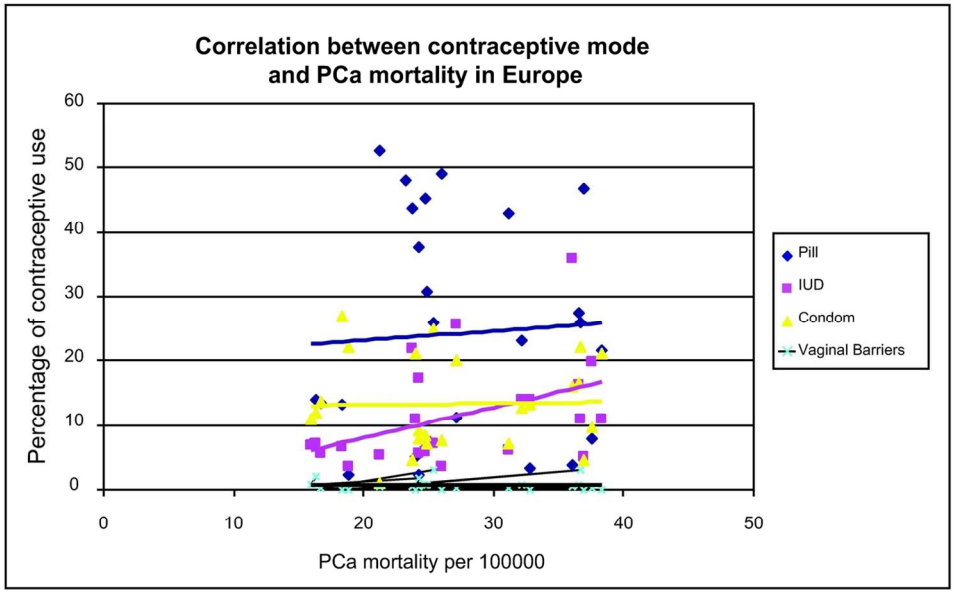

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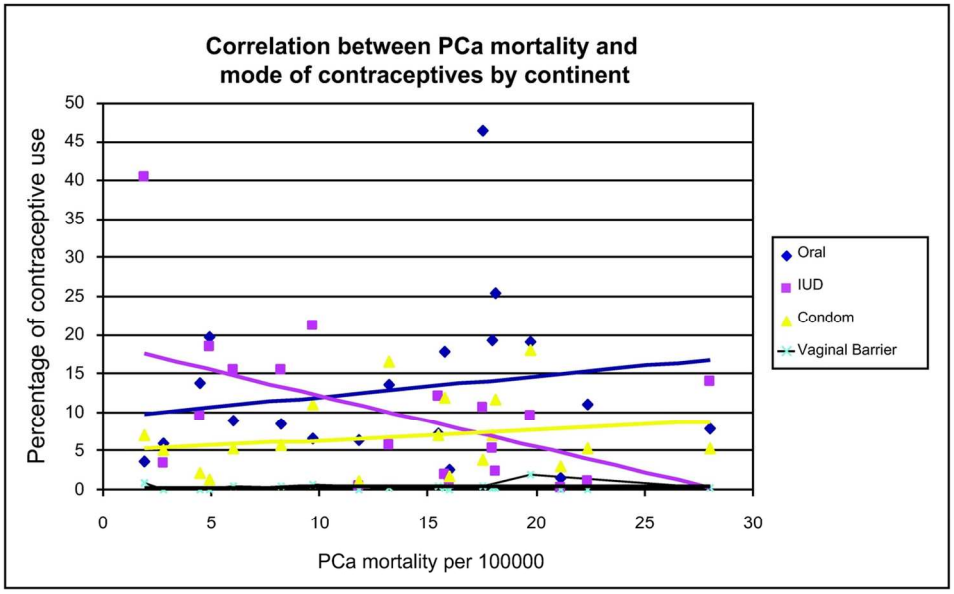
Figure 2C



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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not relevant

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not relevant
		(b) Give reasons for non-participation at each stage	Not Relevant
		(c) Consider use of a flow diagram	Not Relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not Relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not Relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not Relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Relevant
		Cross-sectional study—Report numbers of outcome events or summary measures	Not Relevant
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not Relevant
		(*b*) Report category boundaries when continuous variables were categorized	Not Relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not Relevant
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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