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Oral contraceptive use is associated with prostate cancer: an ecological study

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PRESS RELEASE

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ABSTRACT

Background: Several recent studies have suggested that oestrogen exposure may increase the risk of prostate cancer (PCa).

Objectives: To examine associations between PCa incidence and mortality and population-based use of oral contraceptives (OCs). It was hypothesised that OC by-products may cause environmental contamination, leading to an increased low level oestrogen exposure and therefore higher PCa incidence and mortality.

Methods: The hypothesis was tested in an ecological study. Data from the International Agency for Research on Cancer were used to retrieve age-standardised rates of prostate cancer in 2007, and data from the United Nations World Contraceptive Use 2007 report were used to retrieve data on contraceptive use. A Pearson correlation and multivariable linear regression were used to associate the percentage of women using OCs, intrauterine devices, condoms or vaginal barriers to the age standardised prostate cancer incidence and mortality. These analyses were performed by individual nations and by continents worldwide.

Results: OC use was significantly associated with prostate cancer incidence and mortality in the individual nations worldwide ($r=0.61$ and $r=0.53$, respectively; $p<0.05$ for all). PCa incidence was also associated with OC use in Europe ($r=0.545$, $p<0.05$) and by continent ($r=0.522$, $p<0.05$). All other forms of contraceptives (ie, 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 a nation's wealth.

Conclusion: A significant association between OCs and PCa has been shown. It is hypothesised that the OC effect may be mediated through environmental oestrogen levels; this novel concept is worth further investigation.

ARTICLE SUMMARY

Article focus

- Several recent studies have suggested that oestrogen exposure may increase the risk of prostate cancer (PCa).
- Associations between PCa incidence and mortality and population-based use of oral contraceptives (OCs) have been examined.
- It is hypothesised that OC by-products may cause an environmental contamination, leading to an increased low level oestrogen exposure and therefore higher PCa incidence and mortality.

Key messages

- In this hypothesis generating ecological study, a significant association between female use of OCs and prostate cancer has been demonstrated.

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.

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 oestrogen 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 (OCs) has exploded over the past 40 years and has had a patchy uptake in terms of global utilisation. Emerging literature suggests that OC use may be associated with a variety of medical conditions among consumers, such as atheroembolic disease 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 (EDCs) and their association with diseases of increasing incidence such as breast cancer (men and women), early onset puberty and testicular cancer. EDCs include a variety of compounds used in commercial applications, such as detergents, 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 OCs. In addition, to explore the specific effect of OCs, we also examined these outcomes in association with other modes of contraception.

METHODS

Study design and data sources

This study utilised a geographic or ecological design to identify associations between aggregate use of contraception and rates of prostate cancer. We utilised data from the International Agency for Research on Cancer to retrieve age-standardised rates of country-specific prostate cancer incidence and mortality in 2008.[12] The incidence data are derived from population-based cancer registries. These mostly cover entire national populations but may cover smaller, subnational 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 World Contraceptive Use 2007 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 15–49 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 the 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.

The following information was collected: percentage of woman of reproductive age using OCs, intrauterine devices, condoms or vaginal barriers. The rationale for examining alternate uses of birth control was to examine specificity for OCs, 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 wanted to test this association among a more homogenous group with narrower ranges of both OC use and prostate cancer incidence/mortality.

We also 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 US government officials. However, it is frequently used as a resource for academic research papers.

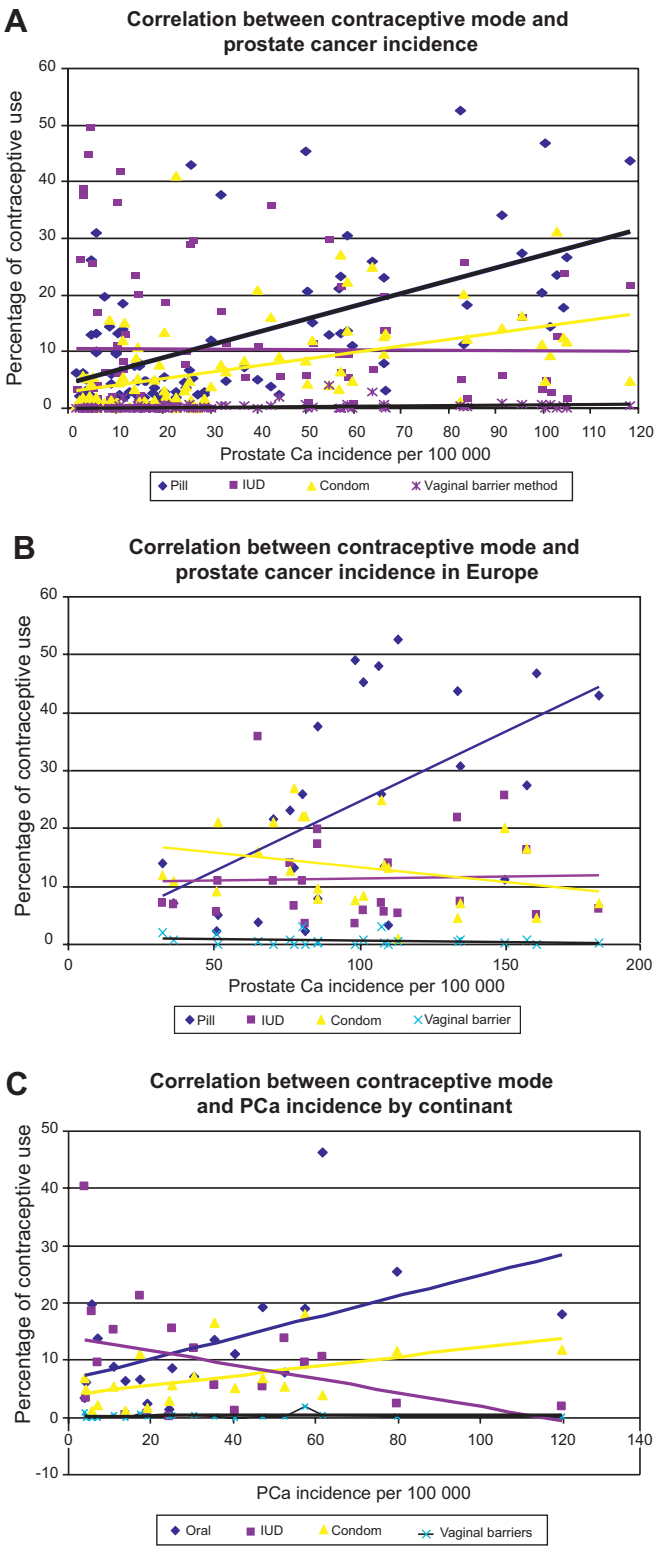

Figure 1 Correlation between prostate cancer (PCa) incidence expressed as age standardised per 100 000 persons and percentage of contraceptive use in women aged 15–49, in individual nations: worldwide (A), in Europe (B), and by continent (C).

Statistical analysis

Pearson correlation was used to associate age-adjusted prostate cancer incidence and mortality rates to the percentage of women using OCs, intrauterine devices, condoms or vaginal barriers. We performed these analyses by individual nations and by continents worldwide. We randomly identified 87 different nations for the survey, ensuring sampling of each continent (the 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 in Africa, 25 of 50 in Asia, 24 of 47 in Europe, and 11 of 23 in America, Australia and New Zealand were also included). We did not use all available countries since we aimed at a equal representation of developed and 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; mortality variables included in our model were: percentage of women of reproductive age using OCs, intrauterine devices, condoms or vaginal barriers; and GDP per-capita in each nation. Probability values <0.05 were deemed significant.

RESULTS

As shown in figure 1A–C, OC use was significantly correlated with prostate cancer incidence in the individual nations worldwide (figure 1A; $r=0.61$, $p<0.05$), in Europe (figure 1B; $r=0.545$, $p<0.05$), and by continent (figure 1C; $r=0.522$, $p<0.05$). All other forms of contraceptives (ie, intrauterine devices, condoms or vaginal barriers) were not correlated with prostate cancer incidence.

Mortality correlated with OC use in the individual nations worldwide (figure 2A; $r=0.53$, $p<0.05$). 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 shows the multivariable analysis of the association of PCa incidence and mortality with mode of contraceptives controlling for GDP per-capita. As shown, both incidence and mortality were associated with OC use even after controlling for an indicator of a country's wealth (adjusted estimate 1.06 (95% CI 0.58 to 1.6) and 0.75 (95% CI 0.31 to 1.1), for incidence and mortality respectively; $p<0.01$ for all).

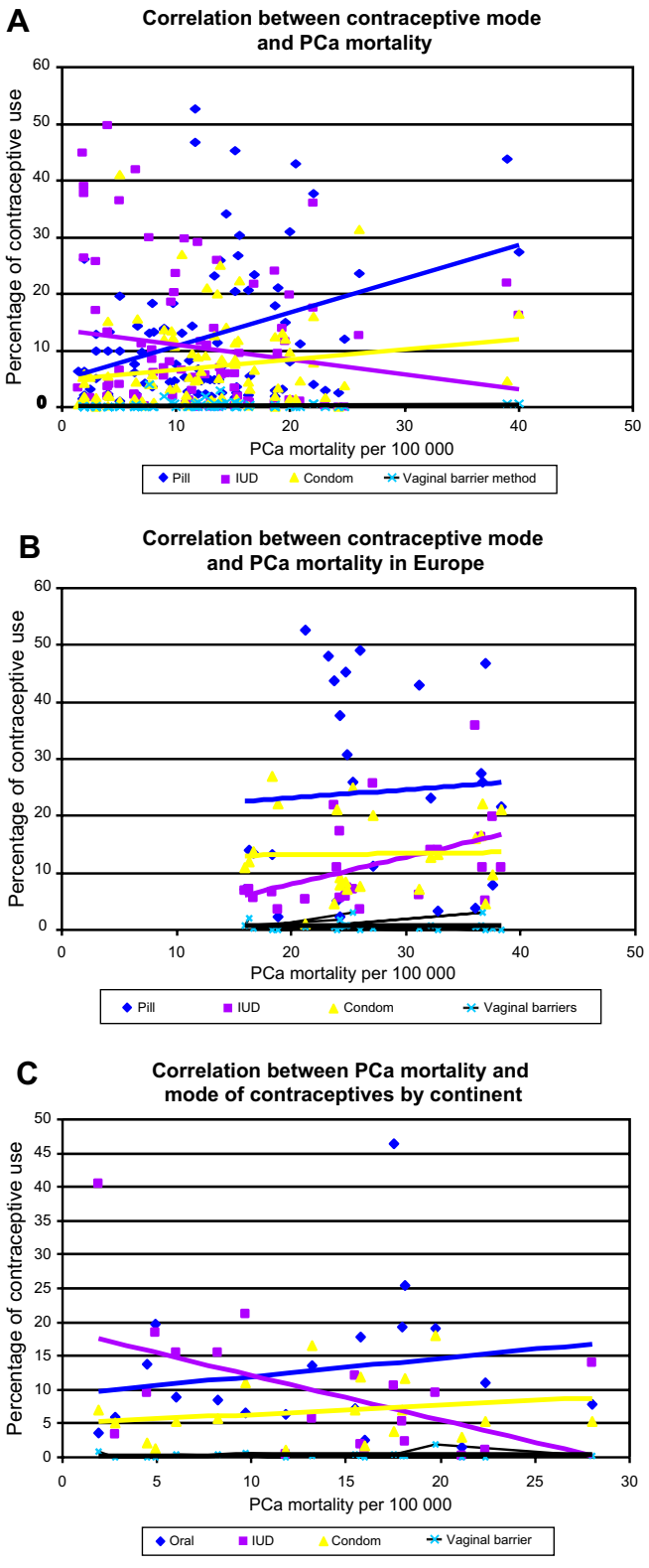

Figure 2 Correlation between prostate cancer (PCa) mortality expressed as age standardised per 100 000 persons and percentage of contraceptive use in women aged 15–49, in individual nations: worldwide (A), in Europe (B), and by continent (C). IUD, intrauterine device.

DISCUSSION

In this study we have shown a strong correlation between the country-specific female OC use and incidence of prostate cancer among worldwide, 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 OC use was independent of GDP as a measure of a country's wealth, and strongest in Europe.

Table 1 Multivariable linear regression of the association of mode of contraception and GDP (a measure of country's wealth) with prostate cancer (PCa) incidence and PCa mortality

	Estimate	95% CI	p Value
PCa incidence			
Oral contraceptive use	1.06	0.58 to 1.6	<0.001
Intrauterine device	0.01	−0.4 to 0.4	0.9
Condom use	0.9	−0.1 to 1.9	0.3
Vaginal barrier	0.07	−4 to 10	0.5
GDP	0.6	0.1 to 1.1	0.055
PCa mortality			
Oral contraceptive use	0.75	0.31 to 1.1	0.06
Intrauterine device	−0.02	−0.4 to 3	0.2
Condom use	0.2	−0.1 to 0.329	0.3
Vaginal barrier	0.01	−2.1 to 2	0.9
GDP	0.16	0.04 to 0.9	0.09

GDP, gross domestic product 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.

This study represents the first systematic analysis of associations between OC use and prostate cancer. It is an ecological study and thus has, as with 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 leukaemia virus-related virus and its discovery in semen has raised this as a possible candidate.[17 19] Clearly more studies are needed. We would hypothesise, 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 OCs. 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 industrialised world are often cited as evidence that widespread exposure of the general population to EDCs has had adverse impacts on human health. OCs in use today can potentially act as EDCs as they frequently contain high doses of ethinyloestradiol, which is excreted in urine without degradation. This can then end up either in the drinking water supply or passed up the food chain.[11] OCs were made publicly available in the 1960s, and have been 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 epidemiological 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 organochlorine insecticide with well defined oestrogenic properties, increases 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 EDCs may affect the unborn child in the state of organogenesis and cause significant genetic or epigenetic malformations.

In contrast, several recent studies have demonstrated that PCa may not be related to endogenous androgens. The Endogenous Hormones and Prostate Cancer Collaborative Group, analysing[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 sulphate, androstenedione, androstanediol glucuronide, oestradiol or calculated free oestradiol. However, this study investigated 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 oestrogen-related genes (CYP11A1, CYP19A1, UGT1A1) and risk of prostate cancer in the Prostate Cancer Prevention Trial. The results indicate that repeat polymorphisms in genes involved in oestrogen biosynthesis and metabolism may influence risk of PCa. Further studies are needed to determine the role of EDCs in PCa.

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 OCs and a higher incidence of prostate cancer. Unfortunately data on worldwide screening tendencies or prostate specific antigen (PSA) use is unavailable. However, we included a multivariable analysis controlling for 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, OC 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.

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

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Competing interests None.

Contributors Both authors have directly participated in the planning, execution or analysis of the study, and have read and approved the final version submitted.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data is available from the corresponding author at: sdmargel@gmail.com

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APPENDIX 1

A. List of countries included in analysis

Kenya
Mozambique
Uganda
Zambia
Zimbabwe
Angola
Cameroon
Central African Republic
Chad
Congo
Gabon
Egypt
Libyan Arab Jamahiriya
Sudan
Botswana
Namibia
South Africa
Benin
Ghana
Mali
Mauritania

Niger
Nigeria
Senegal
Sierra Leone
Togo
China
Japan
Republic of Korea
Afghanistan
Bangladesh
India
Iran (Islamic Republic of)
Kazakhstan
Pakistan
Tajikistan
Turkmenistan
Uzbekistan
Indonesia
Myanmar
Philippines
Thailand
Viet Nam
Israel
Jordan
Lebanon
Oman
Saudi Arabia
Syrian Arab Republic
Turkey
Yemen
Belarus
Czech Republic
Hungary
Poland
Romania
Russian Federation
Slovakia
Ukraine
Estonia
Finland
Latvia
Lithuania
Norway
Sweden
United Kingdom
Albania
Bosnia and Herzegovina
Italy
Portugal
Spain
Belgium
France
Germany
Switzerland
Mexico
Argentina
Bolivia
Brazil
Chile
Paraguay
Peru
Uruguay
Venezuela (Bolivarian Republic of)
Canada
United States of America
Australia
New Zealand

B. List of Continent analysed

Eastern Africa
Middle Africa
Northern Africa
Southern Africa
Western Africa
Eastern Asia
South-Central Asia
South-Eastern Asia
Western Asia
Eastern Europe
Northern Europe
Southern Europe
Western Europe
Caribbean
Central America
South America
Northern America
Australia/New Zealand

Correction

After review of the data it appears that the authors accidentally miscoded several points in the data set, which have resulted in an error in the published article (*BMJ Open* 2011;**1**: e000311. doi:10.1136/bmjopen-2011-000311). In the abstract the year used to retrieve age standardised incidence and mortality rates was the 2008 and not 2007 dataset (the correct year is mentioned in the methods section and in the references), and the number of countries was 88 (as appears in the appendix) and not 87. The Pearson correlation between prostate cancer incidence in nations' world-wide and oral contraceptive use was 0.58 and not 0.61. The Pearson correlation between prostate cancer incidence in Europe and oral contraceptive use was 0.59 and not 0.55. Prostate cancer incidence correlated with condom use in nations worldwide (r=0.48) but not in Europe or by continent. Figure 1A,B have been corrected. In the multivariable mode the adjusted estimates for the association of oral contraceptive use with prostate cancer incidence is 0.65 (95% CI 0.3 to 1.01), p=0.001 (not 1.06 (95% CI 0.58 to 1.6)). Table 1 has been corrected. The correlation of prostate cancer mortality rates with oral contraceptive use was not statistically significant (r=0.16, p=0.1 not 0.53, p<0.05). Figure 2 has been changed. With hindsight, after correcting the data and the analysis, the title of the manuscript would have been less easily misinterpreted if it had been: 'Oral contraceptive use is associated with prostate cancer incidence: an ecologic study'.

Data deposited in the Dryad repository: doi:10.5061/dryad.ff6bd0pq (http://datadryad.org/).

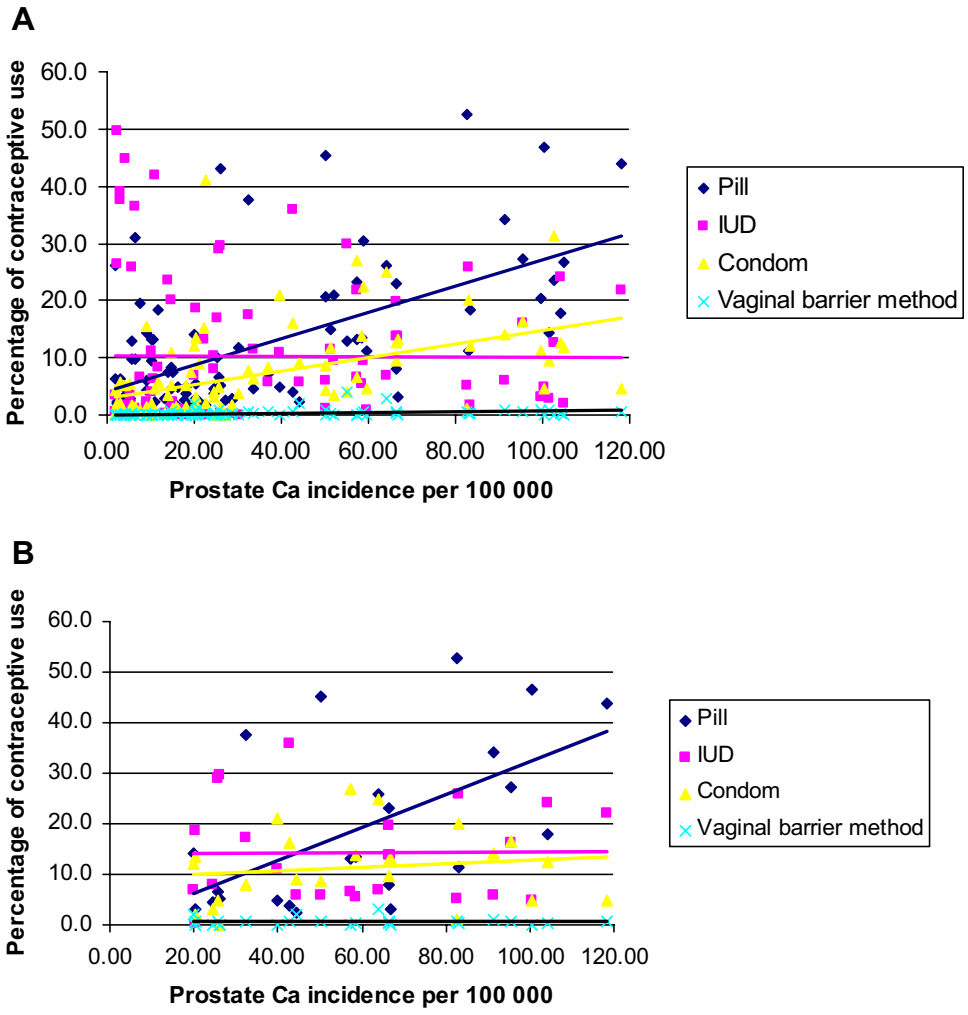

Figure 1 (A) Correlation between contraceptive mode and prostate cancer incidence. (B) Correlation between contraceptive mode and prostate cancer incidence in Europe.

Table 1 Multivariable linear regression of the association of mode of contraception and GDP (a measure of country's wealth) with PCa incidence

	Estimate	95% CI	p Value
Oral contraceptive use	0.65	0.3 to 1.01	0.001
Intrauterine device	−0.12	−0.4 to 1.7	0.46
Vaginal barrier	2.2	−3.6 to 8.2	0.45
Condom use	0.59	0.02 to 1.2	0.04
GDP	0.01	0.009 to 0.011	<0.001

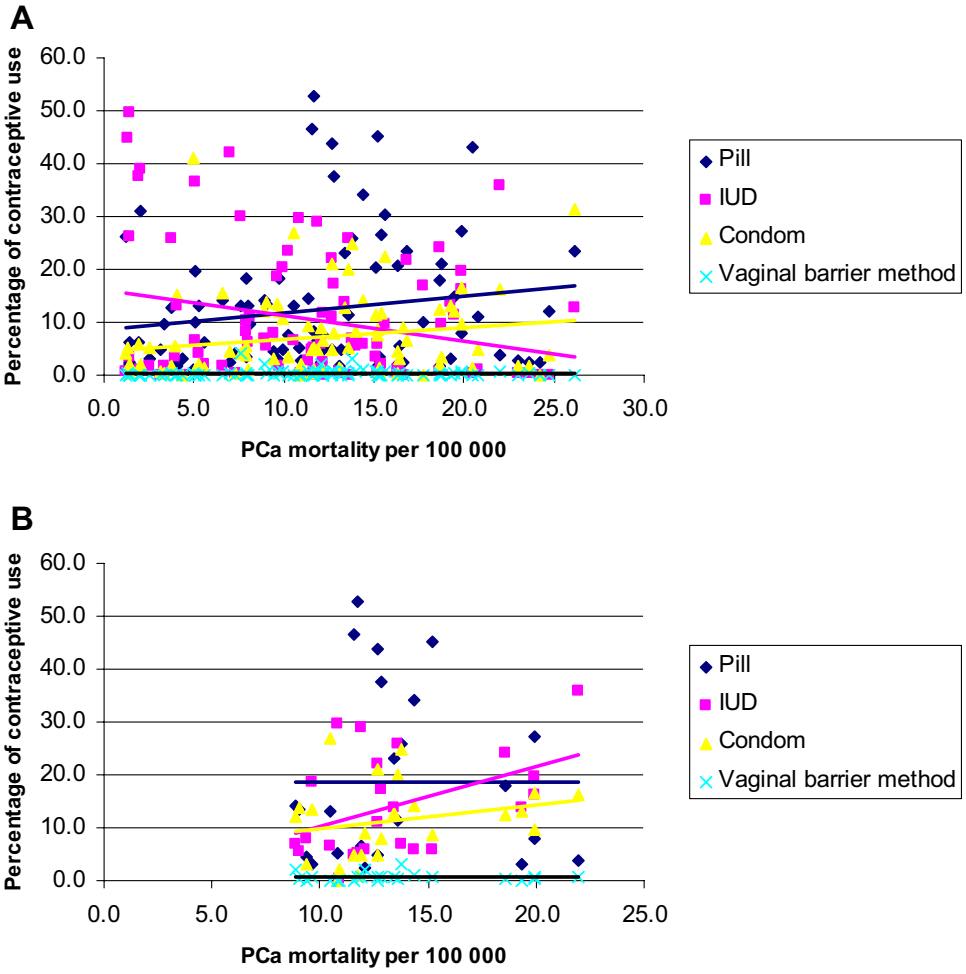

Figure 2 (A) Correlation between contraceptive mode and PCa mortality. (B) Correlation between contraceptive mode and PCa mortality in Europe.

BMJ Open 2012;**2**:e000311corr1. doi:10.1136/bmjopen-2011-000311corr1

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 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not relevant
		(*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.