A case control study of breast cancer risk and exposure to injectable progestogen contraceptives

Methods and patterns of use among controls

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Objective. To describe the patterns of use of injectable progestogen contraceptives (IPCs) among coloured and black women in the Western Cape. These data are part of an ongoing study in the Western Cape, the main aim of which is to explore the relationship between IPCs and breast cancer.

Design. A population-based case-control study of breast cancer risk in relation to the use of IPCs among coloured and black women.

Setting. The Western Cape, including the Cape metropole and surrounding rural areas.

Study subjects. All coloured and black women with newly diagnosed breast cancer, resident in the study area and below age 55 years, who present at either of the two tertiary care hospitals in the Western Cape are recruited. Controls are a sample of hospitalised patients representative of the populations from which the patients are drawn. Cases are frequency-matched to controls according to cross-tabulation of age, ethnic group and residential area in a ratio of approximately 1:3.

Measurements. Questionnaires are administered by trained nurse interviewers. Information is elicited on a wide range of variables, including sociodemographic variables, medical history, family history of breast disease, lifetime history of all methods of contraception and use of non-contraceptive female steroids, reproductive variables, cigarette smoking, alcohol consumption and other potentially confounding variables.

Results. Between January and December 1994, 122 incident cases and 389 controls were enrolled. Ever-use of IPCs among the controls was 72% (N = 280) and use for 5 years or more was 30% (N = 117). Use of IPCs in the distant past was common, with 61% (N = 232) of all controls having initiated use 10 or more years previously. Current use was also high (19%). Other contraceptive methods were used far less commonly.

Conclusion. Coloured and black women in South Africa have been using and continue to use IPCs far more commonly and for longer periods than women anywhere else in the world. It is therefore especially important to evaluate the risk of breast cancer and other health effects of IPCs. The rates of use identified in this study ensure that there will be adequate statistical power to evaluate long-term use, use in the distant past and current use of IPCs.

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Carcinoma of the breast is a common cancer worldwide.[1] Since hormonal contraceptives were introduced in the mid-1960s there has been continued concern that they may increase the risk of breast cancer. For oral contraceptives, almost all of which are combinations of synthetic oestrogens and progestogens, the relationship of use to breast cancer risk has not been resolved, despite multiple rigorous and large-scale studies.[2] Recent evidence has raised the possiblity that long-term use may be related to an increased risk at young ages.[3] Breast cancer risk in relation to hormonal replacement therapy for post-menopausal women, in the form of an unopposed oestrogen, or an oestrogen together with a progestogen, has also been the subject of much attention, again with uncertain results.[4]

The influence of unopposed progestogen, principally depot medroxyprogesterone acetate (DMPA), on the development of breast cancer has received relatively scant attention[5] despite DMPA's being one of the most common means of reversible birth control worldwide. The drug has been widely used in both developing and some developed countries, such as New Zealand.[6] Oral medroxyprogesterone (Provera) is also increasingly being used as the progestogen component of combined hormone (replacement) therapy.

South Africa offers a unique opportunity for investigation of the association between exposure to IPCs and the development of breast cancer. There is an exceedingly high level of long-term use and at the same time the presence, in some regions, of technically advanced facilities for the

agnosis and treatment of breast cancer. In late 1993 a opulation-based case-control study was initiated, with the rimary aim of assessing whether the long-term use (5 years r longer) of IPCs influences the incidence of breast cancer. his paper describes the methods and presents preliminary ata on patterns of use.

Methods

The study region is a geographically defined area in the Western Cape that lies within approximately 150 km of Cape Town. The study population comprises all coloured and black women resident in the study region, aged 19 - 54 years — approximately 126 053 black women and 412 304 coloured women.[7] This population is served by the two major tertiary care hospitals in the Western Cape, both located in Cape Town. Almost all women who develop breast cancer are treated at these institutions. Until recently these hospitals were the only institutions in the area that offered specialised comprehensive treatment for breast cancer, including radiation therapy and chemotherapy.

All incident cases of invasive breast cancer diagnosed for the first time within the previous 6 months among coloured and black women under the age of 55 years are identified at the two tertiary care hospitals. The study is limited to coloured and black women because their level of IPC use has been known to be particularly high, while use among white women has been low. The upper age limit of 54 years is because IPCs (initially DMPA and more recently norethisterone) came into common use in South Africa in the mid-1960s; women older than 54 have had relatively little opportunity for exposure. Patients with carcinoma *in situ* are excluded as are those with a previous history of malignancy at any site. Cases are identified through regular contact with the breast cancer clinics.

Controls, who are hospital patients without breast cancer, are frequency-matched to cases by age (in 5-year age categories), race and area of residence, with a case/control ratio of approximately 1:3. Frequency matching is by recruitment of controls according to cross-tabulation by all three of these covariates. Additional criteria for recruitment of controls are the following: (*i*) diagnoses must be independent of breast cancer risk; (*ii*) the diagnosis resulting in admission must be independent of contraceptive practice. Both criteria require the exclusion of women admitted for benign breast disease, and criterion 2 requires the exclusion of women admitted for conditions such as myocardial infarction or thrombo-embolism, since these conditions are associated with the use of oral contraceptives. In addition, women admitted for obstetric or gynaecological conditions, rheumatoid arthritis, liver cancer and any long-standing debilitating condition are also excluded because these diseases may influence or be influenced by contraceptive practice. Examples of suitable controls include admissions for trauma, acute infections, orthopaedic conditions, acute and other selected surgical conditions, and recently diagnosed malignancies other than those of the female genital tract or liver. Regular rotation through hospital wards at the two tertiary hospitals is carried out in order to identify controls. Interviewers spend 1 week in each ward interviewing suitable controls from rural and urban areas who were admitted within the previous month. Additional rural controls are recruited as required for matching to rural cases of rotation through rural hospitals. Cases and controls must have been resident in the study area for at least 6 of the 12 months preceding diagnosis.

Most cases are interviewed within a week, and all within a month of first presentation at the referral hospital. Cases are interviewed either when they attend a clinic or in the ward at which they are treated as inpatients. Controls are interviewed while they are inpatients. Pathological reports are obtained to confirm the diagnosis for all cases and to determine stage and tumour size. Discharge summaries are reviewed to re-confirm the eligibility of the controls selected by the nurse interviewers.

The interviews are conducted in the subject's home language (Afrikaans, English or Xhosa) by nurses trained in the administration of the questionnaires that were designed and extensively tested in a pilot study. The accuracy of translation of the questionnaire has been confirmed by independent back-translation. To aid recall of contraceptive use, the interviewers compile a calendar of significant personal events (e.g. age at menarche, marriages, divorces, births, miscarriages, sterilisation, age at menopause), and relate periods of contraceptive use to those events. Samples of oral hormonal medications are shown to subjects to facilitate their identification. It is common practice in public sector maternity units in the Western Cape routinely to administer IPCs to women following delivery. Subjects are therefore specifically asked whether or not they received IPCs at these times and whether they were instructed to report for a further contraceptive injection 2 or 3 months later.

DMPA suppresses ovulation for several months when administered by injection.The drug is readministered at 3-monthly intervals and the total duration of exposure in months can therefore readily be measured by multiplying the number of injections by three. The use of injectable norethisterone as an alternative has become more common in the last decade. The total duration of use is similarly defined, except that the interval between injections is 2 months and the multiplication factor is therefore two.

In order to conduct a valid study of breast cancer risk in relation to contraceptive practice, information on a wide range of other variables is being recorded in order to control confounding and estimate possible effect modification. These factors include age; ethnic group; religious affiliation; history of benign breast disease; lifetime history of all methods of contraception; use of non-contraceptive female steroids; reproductive variables (including age at first birth, parity, gravidity, breast-feeding; miscarriages; elective abortions; age at each pregnancy; age at menarche; and age at menopause); weight; height; body shape; cigarette smoking; alcohol consumption; family history of breast cancer in a first-degree relative, and the age at occurrence in that relative; years of education; employment status; and occupation. Exposure to IPCs in the controls will be examined in strata for each of the covariates, and in cases and controls in order to identify possible confounding and effect modification of each of these variables. With multiple regression techniques, it will be possible to adjust for the relevent covariates simultaneously, and obtain adjusted odds ratios for the effect of IPCs on breast cancer risk.

Results

During the first year 122 cases (median age 43 years) and 389 controls (median age 42 years) were enrolled. The rates of ever having used various contraceptives among the controls were 73% for IPCs and 37% for OCs; 21% of women reported having been sterilised, 8% used IUDs, 2% had used condoms and 2% of subjects reported that the male partner had had a vasectomy. Few women (less than 1%) reported using a diaphragm.

Rates of ever having used oral contraceptives are 22% among black controls and 42% among coloured controls. The corresponding figures for use for 5 years or more are 2% and 8%. Patterns of use of OCs will be reported on when additional data have been collected. There were sufficient data to analyse exposure to IPCs among controls in some detail. The rate of ever having used IPCs for coloured women and black women was 71% and 77% respectively. The corresponding figures for 5 years of use or more are 27% and 44%. Table I gives the distribution of use according to duration.

Table I. Duration of use of IPCs by diagnostic category

	Group I	Group II	Group III	All controls
No IPCs	33 (23%)	43 (31%)	33 (28%)	106 (27%)
< 1 year	27 (19%)	23 (16%)	15 (14%)	65 (17%)
1 - 4 years	41 (29%)	30 (21%)	31 (29%)	102 (26%)
5 - 9 years	19 (13%)	26 (19%)	20 (19%)	65 (17%)
10+ years	23 (16%)	18 (13%)	10 (9%)	51 (13%)
Total	143	140	109	389

Group I — infections and acute surgical conditions; group II — elective surgical conditions, neoplasms, gastro-intestinal conditions; group III — trauma and orthopaedic conditions.

Rates of use for less than 1 year, 1 - 4 years, 5 - 9 years and 10 years and more were 17%, 26%, 17% and 13%, respectively. Rates of use were similar in the three diagnostic categories: 29%, 32% and 28% in each control group were exposed to IPCs for 5 years or more.

Exposure to IPCs in the distant past was extremely common; 20% of all controls had initiated use of IPCs 20 or more years previously. Again, the distribution of distant exposure was similar in the three diagnostic categories (Table II). Four per cent of controls reported initiating use of IPCs within the previous 5 years.

Table II. Time since first use of IPCs by diagnostic category

	Group I	Group II	Group III	All controls
Never used	33 (23%)	43 (31%)	30 (28%)	106 (27%)
< 1 year	1 (1%)	1 (1%)	2 (2%)	4 (1%)
1 - 4 years	5 (4%)	4 (3%)	4 (4%)	13 (3%)
5 - 9 years	9 (6%)	10 (7%)	8 (8%)	27 (7%)
10 - 14 years	24 (17%)	25 (18%)	18 (17%)	67 (17%)
15 - 19 years	34 (24%)	30 (21%)	28 (26%)	92 (24%)
20+ years	36 (25%)	27 (19%)	16 (15%)	79 (20%)
Total	142	140	106	388

Same diagnostic groups as for Table I above.

Current use of IPCs or use within the previous year was present in 19% of all controls. Distribution of the time intervals since last use was similar in the diagnostic groups (Table III).

Table III. Time since last use of IPCs by diagnostic category

	Group I	Group II	Group III	All controls
Never used	33 (23%)	43 (31%)	30 (28%)	106 (27%)
Still using or last used < 1 year previously	29 (20%)	19 (14%)	25 (24%)	73 (19%)
1 - 4 years	17 (12%)	19 (14%)	14 (13%)	50 (13%)
5 - 9 years	17 (12%)	21 (15%)	13 (12%)	51 (13%)
10 -14 years	18 (13%)	18 (13%)	4 (4%)	40 (10%)
15 - 19 years	17 (12%)	14 (10%)	16 (15%)	47 (12%)
20+ years	11 (8%)	6 (4%)	3 (3%)	20 (5%)
Total	142	140	105	387

Diagnostic groups as for Tables I and II.

Discussion

There is experimental evidence to suggest that unopposed progestogens, and more specifically DMPA, may increase breast cancer risk.[8] This evidence is derived from experiments on beagle dogs and many observers believe that it is of no relevance to human risk.[8,9] Nevertheless, for many years the findings in beagle dogs were sufficient to persuade the United States Food and Drug Administration (FDA) not to allow registration of DMPA for contraceptive use. That policy was amended in 1992 when DMPA was licensed for contraceptive use in the USA,[10] mainly as a result of epidemiological findings in two studies of DMPA and breast cancer in which no overall increase in the risk was found.[11,12] A more detailed evaluation of the epidemiological evidence reveals a more confusing picture, since different studies have reported decreased risks, no effect or increased risks associated with the use of progestogen-only contraceptives. In a case-control study confined to women below the age of 35 years, conducted in the UK, the use of an oral progestogen was associated with a significant duration-related reduction in the risk of breast cancer.[13] Yet in a study carried out in Costa Rica,[14] DMPA use was associated with an increased risk. However, the UK results are of limited generalisability because breast cancer that occurred after age 35 years was not studied and the Costa Rican study had high attrition rates that limited the interpretability of the data.

Even the two studies that persuaded the FDA to license DMPA were unclear inasmuch as increased risks were identified in subgroups. In one of the studies an increased risk of breast cancer before age 35 years was evident, but not at more advanced ages.[11] In the second study an increased risk was evident for about 4 years after the administration of DMPA but not therafter; in addition that risk was only evident for short-term, but not for long-term, use.[12] When the two studies were pooled the authors reported that the increased risk was a short-term one confined to women who were currently using DMPA or who had used it in the previous 5 years. However, it is

questionable whether pooling of these data is justifiable. A further problem with both studies is that there were insufficient data to evaluate long-term use beyond 5 years, or use in the distant past, e.g. during the teenage years (when the developing breast may be uniquely susceptible).

There is therefore an urgent need for the re-evaluation of breast cancer risk in relation to IPCs, and South African conditions offer a unique opportunity for further study. The levels of exposure to IPCs identified in this study are higher than those previously reported, even in respect of exposures that took place a decade or more previously. In statistical terms, this study will have sufficient power to document or rule out increased risks of the order of 1.5-fold, even for 5 or more years of exposure that took place as much as a decade previously. In addition, the study will have sufficient power to confirm or rule out the possibility that unopposed progestogens used for many years may decrease the risk of breast cancer, as has been suggested in one study. There is excellent power to assess the hypothesis in respect of current use, raised by two previous studies of DMPA and breast cancer.[15]

On the basis of the present findings it is already clear that since the mid-1960s, the use of IPCs, mainly DMPA, has been considerably more common in the South African population than anywhere else in the world. Owing to these high levels of use in South Africa, there is an important public health need to determine whether or not these methods of contraception are safe in terms of cancer and other health risks.

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