

DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study

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Abstract

Objective: To examine any possible links between exposure to DDE (1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene), the persistent metabolite of the pesticide dicophane (DDT), and breast cancer.

Design: Multicentre study of exposure to DDE by measurement of adipose tissue aspirated from the buttocks. Laboratory measurements were conducted in a single laboratory. Additional data on risk factors for breast cancer were obtained by standard questionnaires.

Setting: Centres in Germany, the Netherlands, Northern Ireland, Switzerland, and Spain.

Subjects: 265 postmenopausal women with breast cancer and 341 controls matched for age and centre.

Main outcome measure: Adipose DDE concentrations.

Results: Women with breast cancer had adipose DDE concentrations 9.2% lower than control women. No increased risk of breast cancer was found at higher concentrations. The odds ratio of breast cancer, adjusted for age and centre, for the highest versus the lowest fourth of DDE distribution was 0.73 (95% confidence interval 0.44 to 1.21) and decreased to 0.48 (0.25 to 0.95; *P* for trend = 0.02) after adjustment for body mass index, age at first birth, and current alcohol drinking. Adjustment for other risk factors did not materially affect these estimates.

Conclusions: The lower DDE concentrations observed among the women with breast cancer may be secondary to disease inception. This study does not support the hypothesis that DDE increases risk of breast cancer in postmenopausal women in Europe.

Introduction

Environmental oestrogenic compounds, such as the organochlorines DDT (dicophane (2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane)), polychlorinated biphenyls, and dioxins, have been linked to altered sexual development in various species, to a decrease in semen quality, and to an increased risk of breast cancer in women.¹⁻³ Their weak oestrogenic effects may result from altered metabolism and competition for binding to cytosolic and nuclear receptors of steroid hormones.^{4,5}

Because of their lipophilicity and long half lives, organochlorines accumulate in the food chain.⁶ Typically, consumption of fish, meat, and milk is held responsible for the age related increase in concentrations of DDT and its even more persistent metabolite DDE (1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene) in adipose tissue.⁷ Since the ban on DDT in Western countries 20-25 years ago, DDE concentrations in adipose tissue and mothers' milk dropped in successive cohorts but less so in the generations exposed before the ban.^{6,8,9}

Apart from some early reports,¹⁰⁻¹² one nested case-control study in the United States showed a fourfold increased risk of breast cancer at high plasma DDE concentrations,¹³ which was not confirmed by a larger prospective study, also from the United States.¹⁴ We determined the association between DDE and breast cancer among 606 women from five European countries on the basis of DDE measured in adipose tissue aspirated from the buttocks.

Subjects and methods

This investigation is an extension of the European study on antioxidants, myocardial infarction, and cancer of the breast (EURAMIC). This multicentre case-control study included 347 women with breast cancer from Germany, the Netherlands, Northern Ireland, Switzerland, and Spain as well as 374 population and hospital controls.^{15,16} In short, apparently healthy postmenopausal women, aged 50 to 74 years, with a stable dietary pattern and no history of breast cancer were eligible. To achieve efficiency in study conduct and data analysis we aimed at a similar number of cases and controls by study centre and age using group matching. Incident cases with histologically confirmed ductal breast cancer, primary tumour < 5 cm, axillary lymph nodes stage < N3, and no clinical indication of distant metastases at discharge were included. Response rates among women with cancer were 75% (Germany), 76% (Northern Ireland), 92% (Switzerland), and 97% (Netherlands, Spain). Controls were obtained from the hospital catchment area by using registries of local municipalities (Switzerland and Germany with response rates of 22% and 45%) and general practitioners as the sampling frame (Northern

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Ireland, Netherlands, and Spain with response rates of 46%, 50%, and 91%). Information on factors relevant to breast cancer was obtained by similarly formatted centre specific questionnaires, with a priori specified variables for central data analysis. Procedures for sampling and data collection were approved by local ethics committees in each participant's country. Informed consent was obtained from eligible subjects.

Needle aspirates were taken from the subcutaneous fat of the buttocks in 317 women with cancer and 367 controls.¹⁵⁻¹⁷ For the cancer patients the fat aspirates were taken within seven days after hospital admission. After the exclusion of five subjects for whom relevant background data were missing, fat aspirates of 265 cases and 341 controls were available for laboratory analysis—that is, DDE was analysed in 84% and 93% of the aspirates obtained. This percentage is lower in the cases because for one of the centres the aspirates had to be collected in several hospitals by different staff, less skilled in fat aspiration. To facilitate the standardising and instructing of the skills for fat aspiration, a videotape was prepared and distributed among all centres before the start of the project. In the four other centres this apparently led to good results as sufficient amounts of fat could be aspirated from 91% of the cases and 93% of the controls in these centres. After local storage at -70°C and shipment on dry ice, samples were analysed centrally for vitamins and fatty acids.^{15, 16}

Laboratory analyses of DDE were conducted at the National Institute of Public Health and Environmental Protection (Bilthoven, Netherlands), with sample vials randomised before laboratory analyses and staff blinded to disease status. The initial iso-octane extracts contained the methylated fatty acids and heptadecanoic acid (C17:0) as an internal standard. This solution was subjected to hyphenated chromatography, in which liquid chromatography was coupled on line to capillary chromatography. This analysis was carried out on a commercially available liquid chromatography-gas chromatography system (Dualchrom 2000; Carlo Erba Instrument, Milan, Italy) equipped with a Ni63 electron capture detector. The liquid chromatography injection volume was 50 μl . The on column interface was used to transfer a volume of 200 μl into the column. The chromatographic columns were a liquid chromatography column of 50 mm \times 1 mm internal diameter packed with 3 μm hypersil silica and a DB5MS gas chromatography column (30 m \times 0.32 mm internal diameter, film thickness 0.5 μm). The C17:0 content was determined by gas chromatographic analysis. When the concentration of DDE was below the detection limit ($n = 19$) half the lowest concentration in the remaining samples was entered. The coefficient of variation within each batch varied from 1% to 5% for C17:0 and from 1% to 8% for DDE and between batches from 7% to 8% for C17:0 and from 8% to 11% for DDE. Concentrations of DDE are expressed in micrograms of DDE per gram of fatty acids in the aspirate.

Data analyses were performed with SAS statistical software.¹⁸ Although skewed distributions of DDE required log transformations in data analysis, results presented are geometric means. Crude means as well as means adjusted for age and centre were calculated for DDE and major risk factors for breast cancer. To

identify potential confounders, mean levels of risk factors for breast cancer were compared among fourths of DDE concentration in controls. Odds ratios (and 95% confidence intervals) for breast cancer were obtained from multivariate logistic regression analysis by modelling DDE, firstly in fourths and then as a continuous variable, and contrasting the risk for subjects on the 75th and 25th centiles. In tests for trend, the median DDE concentration in each fourth was used. Interaction terms between DDE and body mass index, waist : hip ratio, fat mass, parity, hormone replacement therapy, oestrogen receptor status, time since menopause, previous benign breast disease, family history of breast cancer, and current alcohol use were tested, but none was significant.

Results

Table 1 shows risk factors among cases and controls. Age was similar because of the matched design. Women with breast cancer had significantly higher body mass indices, waist : hip ratio, age at first birth, and family history of breast cancer. No other significant differences were found.

Among controls, body mass index (kg/m^2) was positively associated with DDE concentration and increased from 24.9 (SD 4.0) in the lowest fourth to 28.2 (4.7) in the highest fourth ($P < 0.01$). Waist : hip ratio increased from 0.83 (0.08) to 0.86 (0.06) ($P = 0.03$). Reported history of benign breast disease differed between fourths of DDE ($P = 0.05$), ranging from 13.1% (10.2%) in the second to 3.6% (10.8%) in the fourth. Current alcohol use was more prevalent in the lowest than in the highest fourth (57.4 (7.9%) *v* 40.2 (8.5%); $P < 0.01$).

Mean DDE concentration was 1.35 $\mu\text{g}/\text{g}$ and 1.51 $\mu\text{g}/\text{g}$ among cases and controls, respectively, a difference of -10.5% , which changed little after adjustment for age and centre (-9.2% ; $P = 0.36$; table 2). Concentrations were lower among cases than among controls in all but one centre (the Netherlands). DDE concentrations ranged from 2.5-fold to 3-fold between countries, being lowest in Northern Ireland and highest in Spain. Within controls, the median exposure in the lowest (0.40 $\mu\text{g}/\text{g}$) versus the highest fourth (5.07 μg) differed 12.5-fold (table 3). The odds ratio for breast cancer, adjusted for age and centre, for the highest versus the lowest fourth of DDE was 0.73, but the test for trend was not significant ($P = 0.16$). Adjustment for body mass index, age at first birth, and current alcohol consumption strengthened the inverse association (P for trend = 0.02), with the odds ratio in the highest fourth showing a significant 52% risk reduction. The largest change in the odds ratio occurred when body mass index was entered into the model, which made further adjustment for waist : hip ratio superfluous. When DDE was modelled as a continuous variable, the odds ratio for a subject at the 75th versus the 25th centile (3.46 *v* 0.86 $\mu\text{g}/\text{g}$) was 0.84 (95% confidence interval 0.73 to 0.97). Further adjustment for waist : hip ratio, history of previous benign breast disease, family history of breast cancer, and years since menopause did not materially affect the risk estimates.

Discussion

Our study did not confirm the hypothesis that DDE concentrations in adipose tissue are higher in women with breast cancer. In contrast, we observed an overall inverse association between DDE and breast cancer, which was consistent in most of the study centres.

Interpretation of results

In the EURAMIC study, we assessed DDE in fat aspirates rather than plasma, and subjects who had lost over 5 kg of body weight in the past year were not eligible. These characteristics are important for diminishing random misclassification and for preventing information bias in the case-control design. Response rates of women with cancer ranged from 75% to 97% compared with 22% to 45% among population controls (Switzerland, Germany) and from 46% to 91% when control recruitment was mediated by general practitioners (see methods).

Case-control differences in the DDE concentrations were largest in the centre that contributed the smaller number of subjects to the dataset (table 2). Although part of this difference may have resulted from a less successful aspiration technique in this centre, it might be due to chance as well, and because of the small number of subjects it will not have affected the main findings and conclusions. Moreover, the case-control differences in DDE concentrations specific for centre were not obviously related to response rates or to control selection procedures.

The overall ratio of the DDE concentration in cases and controls was 0.89 (1.35:1.51; see table 2), and it was slightly closer to 1.0 in the three centres that had higher response rates because controls were obtained by general practitioners (Spain 0.82, Northern Ireland 0.96, Netherlands 1.05) than in the centres that obtained their controls through population registers (ratio in Switzerland 0.89, in Germany 0.68). Although this might suggest some bias towards an inverse association between DDE and breast cancer, multivariate adjustment for age at first birth, alcohol, and body mass index will have attenuated biases resulting from subject recruitment and risk factors for breast cancer. Finally, the observed associations between breast cancer and body mass index, reproductive factors, and familial risk are consistent with those reported in the literature, adding credibility to the internal validity of our results.

The discrepant findings from case-control studies may be attributable to subject recruitment and choice of biomarker. In early studies, DDE concentrations in plasma, mammary fat, or tumours from patients with breast cancer were compared with those in healthy subjects and patients with other diseases.^{10-12 19 20} Although some of these studies reported higher concentrations of DDE among cases, given the study design and small number of subjects (not exceeding 44 cases and 33 controls) it is difficult to regard the conclusions as definitive.

Comparison with other research

Table 4 summarises the main results as well as population and design characteristics of the three largest studies on DDE and breast cancer, including the EURAMIC study. The negative findings from Krieger's prospective study arise from data which, having been

Table 1 Description of study population (EURAMIC breast cancer study 1991-2). Values are means (SD) except for proportions, which are means (SE)

Risk factor	Cases (n=265)	Controls (n=341)	P value for difference
Age (years)	62.3 (6.0)	62.3 (5.5)	0.99
Body mass index (kg/m ²)	27.1 (5.0)	26.3 (4.5)	0.04
Weight : hip ratio	0.87 (0.07)	0.85 (0.08)	0.00
Age at menarche (years)	13.7 (1.8)	13.6 (1.5)	0.75
Age at menopause (years)	48.4 (4.8)	48.5 (5.3)	0.86
Nulliparous (%)	24.3 (2.6)	22.0 (2.2)	0.50
Age at first birth (years)*	26.8 (4.9)	25.5 (4.4)	0.00
Family history (%)	27.3 (2.7)	18.0 (2.1)	0.01
Previous benign breast disease (%)	7.7 (1.6)	6.6 (1.3)	0.58
Smoking (%)	18.2 (2.4)	16.7 (2.0)	0.64
Alcohol (%)	51.3 (3.1)	56.0 (2.7)	0.30

*Among parous women.

Table 2 DDE concentrations in cases and controls by study centre and overall (EURAMIC breast cancer study 1991-2)

Centre	Cases	Controls	Mean DDE concentration (µg/g) (95% CI)*†	
			Cases	Controls
Germany	9	53	1.02 (0.33 to 3.20)	1.70 (1.32 to 2.18)
Netherlands	60	58	1.38 (0.99 to 1.91)	1.32 (0.98 to 1.79)
Northern Ireland	90	95	0.99 (0.78 to 1.26)	1.03 (0.80 to 1.33)
Switzerland	50	71	1.17 (0.80 to 5.98)	1.32 (0.95 to 1.84)
Spain	56	64	2.56 (1.83 to 3.59)	3.13 (2.31 to 4.24)
Overall crude means	265	341	1.35 (1.15 to 1.58)	1.51 (1.31 to 1.73)

* Means and 95% confidence intervals transformed from analysis on log scale.

† Difference (95% CI) adjusted for age and centre=-9.2% (-25.3 to 10.5).

Table 3 Odds ratio of breast cancer for fourths of distribution of DDE concentrations in adipose tissue (EURAMIC breast cancer study 1991-2)

	Fourth*				P for trend
	1	2	3	4	
Median exposure to DDE (µg/g)	0.40	1.41	2.50	5.07	
No of cases/controls	73/85	75/85	63/85	54/86	
Odds ratio adjusted for age and centre (95% CI)	1.00	1.06 (0.68 to 1.68)	0.92 (0.57 to 1.48)	0.73 (0.44 to 1.21)	0.16
Multivariate odds ratio† (95%CI)	1.00	1.14 (0.62 to 2.12)	0.71 (0.38 to 1.34)	0.48 (0.25 to 0.95)	0.02

*Quartiles, based on distribution among controls, were 0.86, 1.89, and 3.46 µg/g.

† Adjusted for age, centre, body mass index, age at first birth, alcohol consumption.

Table 4 Main characteristics and results of three largest studies on DDE and breast cancer

Detail	Krieger et al (1994)	Wolff et al (1993)	EURAMIC (1996)
Population characteristics*:			
Mean age (years)	45†	51	62
Postmenopausal (%)	79	40	100
DDE in blood controls (ppb)	43.1	7.7	2.5‡
Design characteristics:			
Study design	Prospective	Prospective	Case-control
Case group	14 Year follow up	Prevalent cases	Clinical cases
Biomarker	Blood serum	Blood serum	Adipose tissue
No of cases/controls	150/150	58/171	265/341
Main results:			
Odds ratio in fourths§ (95% CI)	1.33 (0.68 to 2.62)	3.68 (1.01 to 13.50)	0.48 (0.25 to 0.95)
Continuous¶ odds ratio (95% CI)	1.0 (0.7 to 1.4)	1.7 (1.2 to 2.5)	0.84 (0.7 to 1.0)

ppb = Parts per billion.

* At time of (initial) assessment of exposure.

† Age at sample collection; average age at diagnosis was 59 years.

‡ Inferred from concentration in adipose tissue, assuming 610-fold lower concentrations in plasma.²¹

§ Adjusted odds ratio, highest v lowest third (Krieger et al), fifth (Wolff et al) and fourth (EURAMIC), respectively.

¶ Comparing women at 75th v 25th centile—that is, 57.3 v 25.8 ppb (Krieger et al), 10.34 v 3.76 ppb (Wolff et al), and 3.46 v 0.86 µg/g (EURAMIC), respectively.

collected before the ban on DDT and many years before diagnosis of breast cancer, showed high concentrations of DDE with a wide range.¹⁴ The results from the two case-control studies relate to exposure levels about 10-fold lower and a range in exposure 5-fold to 6-fold narrower, clearly relating to women who were exposed for a shorter period of their lives.^{13 16}

The small nested case-control study by Wolff et al (table 4) was a preliminary report which used prevalent, subclinical cases, in which blood samples had been taken from the patients six months or less before diagnosis. We used adipose DDE concentrations to obtain a long term preclinical reference period within one week after diagnosis and excluded subjects with clear weight loss, thereby providing a more robust assessment of exposure. Although serum and adipose DDE concentrations are highly correlated in healthy women ($r=0.94$),²² this may not extend to women with disease. Metabolic changes secondary to disease inception but preceding clinical diagnosis may mobilise fat stores, leading to increased plasma concentrations and even to some decrease in DDE concentrations in adipose tissue.

To explain the discrepancy between the Wolff and Krieger papers, it has been postulated that previously higher concentrations of the more potent anti-oestrogen dioxin have masked the risks of the weakly oestrogenic DDE in the Krieger study,²³ but our results do not support this explanation. Similarly, one could argue that the weakly oestrogenic effects of DDE might be measurable only at low background concentrations of endogenous oestrogens—that is, after menopause. No evidence of weaker associations after menopause was reported by Wolff or Krieger, and the inverse association we observed in our study among post-menopausal women does not support this idea either.

As lactation is a major route of excretion of DDE in women, parity and duration of lactation have both been associated with lower concentrations of DDE in women.²⁴⁻²⁷ With the possible exception of prolonged lactation, breast feeding is not considered to provide substantial protection against breast cancer within the populations represented in this study and had not been included in our questionnaires. Therefore, like Krieger et al,¹⁴ we adjusted for parity and age at first birth as proxy variables, but the odds ratio was not materially affected. In the case-control study by Wolff et al, which did provide data on lactation, the positive association between DDE and breast cancer increased by almost 40% after adjustment.¹³ In our data, this would increase the odds ratio of 0.48 (for highest versus lowest fourth of DDE) to about 0.7, consistent with our conclusion of lack of association.

Conclusions

When we consider the characteristics of the epidemiological studies on DDE and breast cancer, the apparently conflicting results may be due to a combination of chance and mobilisation of energy from fat stores in the cases. Although these results do not support complex biological interactions between DDE and other environmental or endogenous (anti)oestrogens, the recent observation of a 1000-fold potentiation by combinations of two environmental oestrogens²⁸ (but not DDE) suggests that these substances may be related to a wide range of health

Key messages

- Organochlorines such as polychlorinated biphenyls and DDT may increase the risk of breast cancer in women
- DDE concentrations among the women with cancer were lower than among the controls, and there was an inverse risk gradient with higher DDE concentrations which remained significant after adjustment for risk factors for breast cancer
- These results are clearly incompatible with an increased risk of breast cancer at increased concentrations of DDE, although associations with other organochlorines cannot be excluded

effects. Whatever the reality, the results of this large case-control study are clearly incompatible with a substantially increased risk of breast cancer among European women with high DDE concentrations.

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Case-control study of oestrogen replacement therapy and risk of cervical cancer

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Abstract

Objective : To examine the relation between use of oestrogen replacement therapy and risk of cervical cancer.

Design : Case-control study.

Setting : Northern Italy.

Subjects : 645 women aged 40-75 years with cervical cancer admitted between 1981 and 1993 to university and general hospitals. The control group consisted of 749 women aged 40-75 years admitted to the same hospitals with acute conditions judged to be unrelated to any of the known or suspected risk factors for cervical cancer.

Main outcome measures : Use of oestrogen replacement therapy and risk of cervical cancer.

Results : 40 cases versus 86 controls had ever used oestrogens, and the corresponding multivariate odds ratio was 0.5 (95% confidence interval 0.3 to 0.8). The odds ratios of cervical cancer decreased with duration of use, being 0.6 (0.4 to 1.1) for less than 12 months' use and 0.5 (0.2 to 1.0) for use for 12 months or more compared with never users. The protection tended to be somewhat stronger for women reporting first oestrogen use before age 50. The odds ratio was 0.9 (0.5 to 1.7) for women who had taken oestrogens within the past 10 years and 0.4 (0.2 to 0.7) for those who had taken them 10 or more years ago.

Conclusion : These findings suggest that exogenous oestrogens do not increase the risk of cervical cancer and may decrease the risk.

Introduction

Convincing epidemiological evidence exists that hormonal factors have a role in the development of cervical cancer. For example, several studies have shown that parity¹⁻³ and use of oral contraceptives^{1,4,5} increase the risk of invasive cervical cancer. These findings suggest that oestrogen-progestin stimulation can

favour, or accelerate, cervical carcinogenesis, possibly through glucocorticoid dependent oncogenic transformation by selected papilloma viruses.⁶ It has also been suggested that this may be a hormone mediated effect on one of the late stages of carcinogenesis.⁷

Little information is available, however, on the separate role of oestrogens and progestogens on cervical carcinogenesis. In particular, few data have been published on the potential relation between oestrogen replacement therapy and risk of invasive cervical cancer.⁸ We present the results of a case-control study of the effects of oestrogen replacement therapy on cervical cancer.

Subjects and methods

The design of this study has been described.³ Briefly, the study was a hospital based case-control investigation conducted in the greater Milan area, Northern Italy, on 645 women aged 40-75 years with histologically confirmed invasive cervical cancer who were admitted during 1981-93 to the obstetrics and gynaecology clinics of the University of Milan, the National Cancer Institute, and the Ospedale Maggiore of Milan (which includes the four largest hospitals in Milan). Of these women, 368 (57%) had squamous cancers and 116 (18%) adenocarcinoma; the 161 (25%) remaining women had another or undefined histological type. The comparison group consisted of 749 women aged 40-75 years with acute conditions judged to be unrelated to any of the known or suspected risk factors for cervical cancer who were admitted to the same hospitals where the cases had been identified (mainly the Ospedale Maggiore and several specialised university clinics). The control women were therefore from similar catchment areas to the cases. Controls were not individually matched but selected within comparable age strata of cases. They were not included if they were admitted for gynaecological, hormonal, or

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Table 1 Distribution of 645 cases of cervical cancer and 749 controls according to selected characteristics, Italy 1981-93

	No (%) of cases	No (%) of controls	Odds ratio (95% CI)*
Age (years):			
<45	93 (14)	75 (10)	—
45-54	204 (32)	219 (29)	—
55-64	212 (33)	254 (34)	—
≥65	136 (21)	201 (27)	—
Education (years):			
<7	464 (72)	461 (62)	1†
7-11	113 (18)	188 (25)	0.8 (0.6 to 1.1)
≥12	68 (11)	100 (13)	0.8 (0.5 to 1.2)
Menopausal status:			
Premenopausal or menopausal	230 (36)	172 (23)	1†
Postmenopausal	415 (64)	576 (77)	0.6 (0.4 to 0.8)
Unknown	0	1 (1)	—
Parity:			
0	65 (10)	122 (16)	1†
1	125 (19)	190 (25)	1.1 (0.7 to 1.7)
≥2	451 (70)	437 (58)	2.0 (1.3 to 3.1)
Unknown	4 (1)	0	—
No of sexual partners:			
0	10 (2)	41 (5)	0.3 (0.1 to 0.7)
1	477 (74)	598 (80)	1†
2	84 (13)	68 (9)	1.8 (1.2 to 2.6)
≥3	67 (10)	32 (4)	3.5 (2.1 to 3.8)
Unknown	7 (1)	10 (1)	—
Oral contraceptive use:			
Never	584 (91)	701 (94)	1†
Ever	61 (9)	48 (6)	1.4 (0.9 to 2.2)
Lifetime No of cervical smear tests:			
0	407 (63)	257 (34)	1†
1	94 (15)	105 (14)	0.5 (0.3 to 0.7)
2	34 (5)	62 (8)	0.3 (0.2 to 0.5)
≥3	105 (16)	313 (42)	0.2 (0.1 to 0.3)
Unknown	5 (1)	12 (2)	—
Smoking status:			
Never	454 (70)	538 (72)	1†
Ever	191 (30)	211 (28)	1.1 (0.9 to 1.5)
Social class:			
Low	260 (40)	311 (42)	1†
Medium	242 (38)	291 (39)	1.2 (0.9 to 1.6)
High	32 (5)	69 (9)	0.8 (0.5 to 1.3)
Unknown	111 (17)	78 (10)	—

*Multivariate estimates including the listed variables except education calendar plus year at interview.

†Reference category.

neoplastic diseases or had had a total hysterectomy. Of the 749 controls, 202 (27%) were admitted for trauma (mostly fractures and sprains), 270 (36%) had non-traumatic orthopaedic disorders (mostly lower back pain and disc disorders), 97 (13%) surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), and 180 (24%) other illnesses such as ear, nose, and throat or dental disorders. Less than 2% of eligible women (cases and controls) refused to be interviewed.

The structured questionnaire included information on personal characteristics and habits; education and other socioeconomic factors; general lifestyle habits such as smoking and alcohol and coffee consumption; a few indicators of sexual habits; gynaecological and obstetric data; number of cervical smears; related medical history; and lifetime use of oral contraceptives, hormonal replacement therapy in menopause, and female hormone preparations for other indications. The time and duration of each episode of use and brand name were registered, whenever available. Lists

of the most common female hormone preparations (covering over 90% of those marketed over the past two decades) were provided to assist recall.

All interviews were conducted in hospital. The same questionnaire was used for cases and controls, and the same interviewers interviewed cases and controls.

Analysis of data

We calculated odds ratios of cervical cancer and the corresponding 95% confidence intervals for various measures of use of oestrogen replacement therapy after adjustment for age.⁹ We also used unconditional multiple logistic regression, fitted by the method of maximum likelihood, including terms for age in quinquennia, calendar year at interview, social class, parity, number of sexual partners, oral contraceptive use, lifetime number of cervical smears, smoking habits, menopausal status, and various characteristics of oestrogen replacement therapy use.¹⁰

Results

Table 1 gives the distribution of cases and controls according to age and selected risk factors for cervical cancer. Cases reported more sexual partners and births than controls and significantly fewer cervical smear tests.

Table 2 gives the relative risks for use of oestrogen replacement therapies. Forty cases versus 86 controls had ever taken oestrogens, and the corresponding multivariate odds ratio was 0.5 (95% confidence interval 0.3 to 0.8). Five cases and six controls reported combined oestrogen and progestogen use. The odds of cervical cancer fell with duration of use, being 0.6 (0.4 to 1.1) for use for under 12 months and 0.5 (0.2 to 1.0) for 12 months or more compared with never users. The protection tended to be somewhat stronger for women reporting first oestrogen use before the age of 50. The odds ratio was 0.9 (0.5 to 1.7) for women who had taken oestrogens within the past 10 years and 0.4 (0.2 to 0.7) for those who had taken them 10 or more years ago.

Discussion

This is one of few epidemiological studies on a meaningful number of subjects that provides reassuring information on oestrogen use and cervical carcinogenesis. The potential limitations of this study should, however, be considered. Firstly, the study was hospital based, with subjects collected from the main general and teaching hospitals in the greater Milan area. Although the study protocol indicated that all new consecutive cases should be interviewed, the design was not strictly population based, and it is likely that some subjects did not enter the study (for instance, because they were not present in the ward at the time of the interviewer's visit). Furthermore, women admitted to general and teaching hospitals are different from those treated in private or smaller institutions in terms of sociodemographic characteristics, and social class is related to use of oestrogen replacement therapy.¹¹

Another important concern is the inclusion in the comparison group of subjects with orthopaedic

diseases or trauma. Women with fractures or sprains may represent a group unusually active and therefore fitter than the cases. Alternatively, they may be selectively oestrogen deficient. These potential biases might, however, tend to reduce the protective effect of oestrogen observed in this analysis. We found no difference in the estimated odds ratio when the analysis was conducted after exclusion of controls with orthopaedic diseases or trauma (multivariate odds ratio for ever *v* never users 0.6, 95% confidence interval 0.3 to 1.1). Another potential limitation of this study is the low prevalence of menopausal replacement treatment in the population, which hampered detailed analysis of subgroups and interactions and might be the cause of selective mechanisms. However, the proportion of women taking oestrogen in the series was consistent with national data in Italy.¹²

With regard to other potential sources of bias, participation was almost complete, and there is no reason to suggest differential recall of hormone use by cases and controls. If anything, women with cervical cancer would be more likely (rather than less) to recall taking female hormones. Furthermore, the hospital based design may improve the comparability of drug recall by cases and controls.¹³ In addition, adjustment for several potential confounding factors did not substantially modify the odds ratios.

More accurate adjustment for confounding could further reduce the apparent association between oestrogens and risk of cervical cancer. However, the inclusion of terms for education and age at menopause, which may well imply overadjustment, gave an odds ratio of 0.7 (0.4 to 1.0).

Association with cervical cancer

The inverse association between oestrogen replacement therapy and cervical cancer may derive from the fact that women receiving oestrogen replacement therapy are screened more frequently than the background population. Thus precancerous lesions (dysplasia and carcinoma in situ) could be diagnosed and treated. However, the inclusion of number of smear tests in the multivariate analysis did not change the estimated relative risks.

Determination of the role of oestrogen replacement therapy in the onset of invasive cervical cancer is important to the understanding of the actions of oestrogens and progestogens. Human papillomavirus

Table 2 Distribution of 645 cases of cervical cancer and 749 controls according to use of oestrogen replacement therapy, Italy 1981-93

	Cases	Controls	Odds ratio (95%CI)	
			Adjusted for age	Fully adjusted*
Use of oestrogen replacement therapy:				
Never	605	663	1†	1†
Ever	40	86	0.5 (0.3 to 0.8)	0.5 (0.3 to 0.8)
Duration of use (months):				
<12	28	50	0.6 (0.4 to 1.0)	0.6 (0.4 to 1.1)
≥12	12	30	0.5 (0.2 to 0.9)	0.5 (0.2 to 1.0)
Unknown	0	6	—	—
χ^2 for trend			8.01 (P≤0.01)	6.42 (P≤0.01)
Age at first use (years):				
<50	21	54	0.5 (0.3 to 0.8)	0.4 (0.2 to 0.7)
≥50	19	31	0.7 (0.4 to 1.3)	0.8 (0.4 to 1.5)
Unknown	0	1	—	—
Time since last use (years):				
<10	23	34	0.7 (0.4 to 1.3)	0.9 (0.5 to 1.7)
≥10	17	46	0.5 (0.3 to 0.8)	0.4 (0.2 to 0.7)
Unknown	0	6	—	—

*Adjusted for age, calendar year at interview, number of sexual partners, parity, oral contraceptive use, lifetime number of cervical smear tests, social class, smoking, menopausal status, and various measures of oestrogen replacement therapy.

†Reference category.

16, the most important cause of cervical cancer, contains a progesterone/glucocorticoid response element upstream to the common E6/E7 promoter,¹⁴ and progesterone enhances the ability of the viral DNA to transform cells.¹⁵ In fact, papillomavirus lesions are exacerbated during pregnancy¹⁶ and risk of cervical cancer is increased by oral contraceptives and pregnancy when progesterone levels are high.^{1 3 4 17} Oestrogen increases human papillomavirus expression by upregulation of the progesterone receptor.¹⁸ However, lack of progesterone in postmenopausal women may explain the lack of adverse effect or even the protection by oestrogen replacement therapy. Our results agree with those from a Swedish cohort study of the long term effect of oestrogen replacement therapy on cancer in hormonal target organs which reported a lower risk of cervical cancer in women receiving oestrogen treatment.⁸

In conclusion, although our findings suggest that exogenous oestrogens do not increase the risk of cervical cancer, the biological interpretation is not obvious. In general, epidemiological results for cervical cancer show an opposite pattern to those of endometrial cancer.¹⁹ This may support a favourable effect of oestrogens (which increase the risk of endometrial cancer¹⁹) on cervical carcinogenesis. Further studies on the effect of oestrogen on cervical carcinogenesis are clearly warranted.

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Conflict of interest: None.

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Key messages

- Although hormonal factors are thought to be important in the development of cervical cancer, few data exist on the role of oestrogen replacement therapy
- In this case-control study women who had taken oestrogen replacement therapy had no higher risk of cervical cancer than women who had not, and the risk may even have been slightly reduced
- The odds of cervical cancer decreased with duration of use
- The reduced risk seems to persist for 10 years or more

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Retrospective study of doctors' "end of life decisions" in caring for mentally handicapped people in institutions in the Netherlands

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Abstract

Objectives: To gain insight into the reasons behind and the prevalence of doctors' decisions at the end of life that might hasten a patient's death ("end of life decisions") in institutions caring for mentally handicapped people in the Netherlands, and to describe important aspects of the decisions making process.

Design: Survey of random sample of doctors caring for mentally handicapped people by means of self completed questionnaires and structured interviews.

Subjects: 89 of the 101 selected doctors completed the questionnaire. 67 doctors had taken an end of life decision and were interviewed about their most recent case.

Main outcome measures: Prevalence of end of life decisions; types of decisions; characteristics of patients; reasons why the decision was taken; and the decision making process.

Results: The 89 doctors reported 222 deaths for 1995. An end of life decision was taken in 97 cases (44%); in 75 the decision was to withdraw or withhold treatment, and in 22 it was to relieve pain or symptoms with opiates in dosages that may have shortened life. In the 67 most recent cases with an end of life decision the patients were mostly incompetent (63) and under 65 years old (51). Only two patients explicitly asked to die, but in 23 cases there had been some communication with the patient. In 60 cases the doctors discussed the decision with nursing staff and in 46 with a colleague.

Conclusions: End of life decisions are an important aspect of the institutionalised care of mentally handicapped people. The proportion of such

decisions in the total number of deaths is similar to that in other specialties. However, the discussion of such decisions is less open in the care of mental handicap than in other specialties. Because of distinctive features of care in this specialty an open debate about end of life decisions should not be postponed.

Introduction

The life of mentally handicapped people is usually strongly influenced by the care of others because most of them are dependent on help with all types of activities. Also, many of the decisions of other people have repercussions on their way of living and dying, an important example being decisions at the end of life that might hasten death ("end of life decisions"). Six years ago data from the Netherlands (published in the so called Rimmeling report) offered insight into the end of life decisions made by doctors in hospitals, family practice, and nursing homes but not by doctors caring for mentally handicapped people.^{1,2} Recently, the study was repeated,³ but, again, there were no specific data on mental handicap. How many people in the Netherlands are mentally handicapped is unknown,⁴ but about 31 000 people live in 136 institutions.⁵ Until recently, end of life decisions by doctors caring for mentally handicapped people have been discussed only among people directly concerned with a specific case. One of the reasons for the lack of public debate is that there is no insight into what is happening. We therefore performed a nationwide retrospective study of doctors' end of life decisions for mentally handicapped patients in institutionalised care, with the aim of discovering what type of decisions had been

Table 1 Incidence of types of end of life decision in mentally handicapped people in institutions. Values are numbers (percentages) of deaths

	All deaths (n=859)	Deaths in 1995 (n=222)
End of life decision:		
Non-treatment	254 (30)	75 (34)
Pain and symptom relief	92 (11)	22 (10)
Euthanasia*	4 (0.5)	0
No end of life decision	506 (59)	124 (56)
Unknown	3 (0.3)	1 (0)

*By lethal injection.

taken, the prevalence of such decisions, and the important aspects of the decision making process.

Subjects and methods

The study population consisted of doctors. Although nurses and the patients' representatives usually participate in decision making, the doctor has final responsibility for medical decisions. There is no official registry of doctors working in the care of mentally handicapped people but most are members of one association. This association gave us its membership list, which contained 224 names.

Questionnaire survey

We drew a sample at random. To reach the number of interviews envisaged we had to draw 142 names. The people selected had to be currently working in the care of mentally handicapped people. Twenty six failed to satisfy this criterion; 15 others were untraceable or unable to participate because they had been ill for a long time. Twelve of the 101 people selected who satisfied the selection criterion and could be traced refused to participate. The 89 doctors reported all deaths of patients for whom they were the attending physician that occurred from 1 March 1991 to 1 March 1996. When less than five years were covered the doctor indicated the actual period. Deaths in hospital and deaths occurring while the respondent was working as a locum were excluded. Eighty nine doctors completed a questionnaire, which comprised six questions for each case, including whether an end of life decision had been taken. Doctors were recommended to use the patients' files while filling in the questionnaire. To estimate annual absolute numbers, we used a weight of 1.79 on the basis of the proportion of doctors represented in the sample.

Interviews

Sixty eight doctors mentioned at least one case in which they had taken an end of life decision, and they were invited to be interviewed about the most recent such death. One refused. Finally, 67 interviews took place between March and June 1996. The interviews were conducted by eight trained interviewers. All of them had experience as a doctor in caring for mentally handicapped people. The interviews lasted between one hour and two and a half hours.

The decisions we studied were withholding and withdrawing life prolonging treatments (non-treatment decisions), relieving pain and symptoms with opiates in dosages that may have shortened life, and ending life by giving lethal drugs (euthanasia by lethal injection). The interview schedules contained many

questions identical with those in the Rummelink questionnaire.^{1,2} Because most mentally handicapped patients are incompetent, a refinement was made about the patient's request. We asked in detail about patients' other actions such as non-autonomous requests or non-verbal communication. Examples of non-autonomous requests were patients saying that they wanted to go to heaven or that they wanted to be left alone. Non-verbal communication included actions of the patient that were interpreted by the doctor or others as a wish to die or stop treatment—for example, constantly removing a feeding tube or resisting all medical treatment.

Mental handicap and diseases were classed according to ICD-10 (international classification of diseases, 10th revision).

Results

Reported deaths

No patient had died in the previous five years for 10 of the 89 respondents, while the remaining 79 doctors reported 859 deaths in an average period of 4.7 years. Of these 79 doctors, 11 had not taken an end of life decision and 68 had taken such a decision in 350 out of 859 cases (41%); 254 were decisions to withhold or withdraw treatment, 92 were to relieve pain and symptoms with opiates, and four were to end life with a lethal drug (table 1).

The number of reported deaths differed considerably from year to year. However, the proportions of the various types of decisions were similar. We estimated absolute numbers for 1995 on the basis of 222

Table 2 Characteristics of patients in most recent cases of deaths in which end of life decision was taken. Values are numbers (percentages) of deaths

	Type of end of life decision		
	Non-treatment (n=44)	Pain and symptom relief (n=20)	All (n=67)*
Sex:			
Male	21 (48)	10 (50)	33 (49)
Female	23 (52)	10 (50)	34 (51)
Age (years):			
0-49	15 (34)	8 (40)	25 (37)
50-64	16 (36)	10 (50)	26 (39)
65-79	10 (23)	1 (5)	12 (18)
≥80	3 (7)	0	3 (5)
Unknown	0	1 (5)	1 (1)
Degree of mental handicap:			
Mild	3 (7)	1 (5)	4 (6)
Moderate	17 (39)	10 (50)	29 (43)
Severe	11 (25)	4 (20)	15 (22)
Profound	12 (27)	3 (15)	16 (24)
Unknown	1 (2)	2 (10)	3 (5)
Diagnosis†:			
Cancer	8 (18)	8 (40)	16 (24)
Diseases of nervous system‡	30 (68)	14 (70)	47 (70)
Diseases of respiratory system	17 (39)	11 (55)	31 (46)
Diseases of digestive system¶	19 (43)	5 (25)	26 (39)
Other diseases	27 (61)	3 (15)	34 (51)
Patient's competency:			
Incompetent	40 (91)	20 (100)	63 (94)
Competent	4 (9)	0	4 (6)

*Including three cases of euthanasia by lethal injection.

†More than one reply could be given to this question.

‡Including stroke and dementia.

¶Including endocrine, nutritional, and metabolic diseases.

Table 3 Reasons why end of life decision was taken in most recent deaths. Values are numbers (percentages) of deaths

	Types of end of life decision		
	Non-treatment (n=44)	Pain and symptom relief (n=20)	All (n=67)*
Request by patient:			
Explicit	2 (5)	0	2 (3)
Non-autonomous	6 (14)	1 (5)	7 (10)
Non-verbal communication	12 (27)	4 (20)	16 (24)
None	24 (55)	15 (75)	42 (63)
Most important reason for decision:			
No chance of improvement	9 (21)	2 (10)	11 (16)
Pain and suffering of the patient	7 (16)	10 (50)	19 (28)
Life would be needlessly prolonged	8 (18)	3 (15)	12 (18)
All medical treatment had become futile	7 (16)	2 (10)	9 (13)
Wish of patient	4 (9)	0	4 (6)
Wish of relative or representative	2 (5)	0	2 (3)
Low quality of life	5 (11)	1 (5)	6 (9)
Undignified dying	1 (2)	2 (10)	3 (5)
Other	1 (2)	0	1 (1)
Intention of doctor:			
Had taken into account probability that death would be hastened	33 (75)	20 (100)	53 (79)
Partly to hasten death	9 (21)	0	9 (13)
To hasten death	1 (2)	0	4 (6)
Unknown	1 (2)	0	1 (1)
Estimated amount of life shortening:			
None	11 (25)	9 (45)	20 (30)
<24 Hours	1 (2)	4 (20)	5 (7)
1 Week at most	7 (16)	4 (20)	14 (21)
1-4 Weeks	13 (29)	0	13 (20)
1-6 Months	6 (14)	2 (10)	8 (12)
>6 Months	4 (9)	1 (5)	5 (7)
Unknown	2 (5)	0	2 (3)

*Including three cases of euthanasia by lethal injection.

Table 4 Process of decision making in most recent deaths in which end of life decision was taken. Values are numbers (percentages) of deaths

	Type of end of life decision		
	Non-treatment (n=44)	Pain and symptom relief (n=20)	All (n=67)*
Doctor discussed decision with†:			
Patient	2 (5)	0	2 (3)
Colleague(s)	28 (64)	16 (80)	46 (69)
Nursing staff	39 (89)	19 (95)	60 (90)
Patient's relative or representative	35 (80)	13 (65)	50 (75)
Educationalist	18 (41)	2 (10)	21 (31)
No one	3 (7)	0	3 (5)
Consensus about decision with all discussants	40 (91)	20 (100)	63 (94)

*Including three cases of euthanasia by lethal injection.

†More than one reply could be given to this question.

reported deaths and the distribution of decisions to end life for that year. This resulted in an estimated total of 397 deaths. For these deaths we estimated that there would be 135 decisions to withhold treatment, 40 decisions to relieve pain and symptoms with opiates, and 222 deaths with no end of life decision. Although we found no decisions to end a patient's life with a lethal injection in 1995, we assumed that one or two of these decisions would have occurred in that year on the basis of the four cases in the whole sample.

Interviews

Sixty seven doctors described the most recent death in which they had taken an end of life decision (tables 2, 3 and 4). Most doctors were trained as general

practitioners (49) and were experienced, having spent an average of 13 years working in this specialty. Thirty six doctors said that they considered themselves to be part of a religious community. Most of the people who had died were under 65 years old, and almost all were considered by the doctor to be incompetent (table 2). They lived in 51 institutions with an average number of 427 residents. Many had diseases of the nervous and digestive systems. Two patients explicitly asked to die. Twenty three doctors said that they had noticed non-autonomous requests and relevant non-verbal communication (table 3).

The most common reason for taking the decision was the pain or suffering of the patient (19 doctors; table 3). In 46 cases the doctor discussed the decision with a colleague. Nurses were almost always consulted (60). Relatives or representatives were less often brought in (50), and consultation with the patient was reported in two cases (table 4).

Three cases of euthanasia were reported. These are included in the third column of tables 2, 3, and 4. The patients in these cases had severe illnesses, including severe heart problems (two patients), tetraplegia, severe epilepsy, and recurrent pneumonia (two patients). In two cases the suffering of the patient had increased substantially before the decision was taken, and the doctors saw no more options to alleviate this suffering. In the other case the doctor mentioned that the terminal phase had started. The doctors estimated that the lives of the patients were shortened by one week at most in all cases. All of them were incompetent and did not express their wishes about the decision. One patient, however, had refused hospital care a year before the decision, when he could still communicate. The doctors consulted a colleague or the nursing staff, or both, in all cases, and two doctors discussed the decision with the patient's relative or representative. Deaths were reported as natural in all cases.

Discussion

The study included more than half of all doctors caring for mentally handicapped people in institutions, and the number of refusals was low. The doctors were asked to report only the deaths of patients for whom they were the attending physician. We believe that the questions were answered reliably because most doctors had the case files with them at interview. The distribution of the types of end of life decisions overall and in 1995 is similar. Our estimated total number for 1995 is close to the 412 deaths reported by the Dutch association for care of the mentally handicapped for 1994 (which is currently the most recent number available).⁶ A limitation of our study is the focus on the last end of life decision. This ignores the fact that such decisions are the result of a process rather than instantaneous.

Our results show that end of life decisions are an important aspect of care for mentally handicapped people. We found no comparable studies in this specialty. A recent study on medical practices at the end of life found that an end of life decision had been taken in 43% of deaths,³ a proportion that is nearly identical with the 41% that we found overall. This similarity might suggest that the debate in the care of mentally handicapped people is similar to that in other specialties. However, distinctive features of this specialty

make separate discussion necessary. Professionals caring for mentally handicapped people have long term relationships with patients. Nurses' observations of the communication and needs of patients are important in decision making. Not only nurses but also representatives of the patient should be included in decision making. Until now, only autonomous requests by competent patients were considered important in end of life decisions. This is probably because the idea of autonomy is paramount. Moreover, when a decision has far reaching consequences, as in end of life decisions, more stringent requirements for competency should be applied.^{7,8} We think that regardless of competency, all expressions that might indicate the patient's wishes are important. Relevant expressions that are non-autonomous in the strict sense were noticed in 34% of our cases. Therefore, the role of communication with incompetent patients should be reconsidered.

The amount of time that life was shortened because of non-treatment in our study seems to be lower than that found in nursing homes in 1991 (life was shortened by 1-6 months in 32% of cases¹ v 14% (6/44) of cases in our study (table 3)). This suggests that end of life decisions are taken later in the course of illness in mentally handicapped people. An explanation could be that patients who are mentally handicapped are cared for in institutions, and the handicaps are usually not progressive lethal diseases. Also, doctors could be more reserved in deciding to hasten death in such patients.

Because of the distinctive features of care for mentally handicapped patients we believe that the difference in openness of debate between this and other specialties should be removed. A public discussion that resonates more fully with the predicaments of caring for mentally handicapped people could greatly contribute to the quality of care at the end of life of these patients.

We thank all the doctors who participated for their willingness to provide data for the study; Dr Paul J van der Maas for his contribution to the manuscript; Dr Hans van den Bergh, Ms Dieta

Key messages

- Little is known about doctors' decisions at the end of life that might hasten death in the care of mentally handicapped patients
- This study shows that these end of life decisions are an important aspect of care of mentally handicapped people in institutions, occurring in around 40% of deaths
- As is the case in other specialties, a public debate about such decisions could greatly contribute to the quality of care for mentally handicapped patients
- The role of communication with patients should be reconsidered to draw attention to the expressions of incompetent patients

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Any questions

Ultraviolet light for psoriasis

Where does the balance of advantage lie in the effect of ultraviolet light for people with psoriasis?

Approximately 80% of people with psoriasis will observe that their psoriatic plaques are improved by exposure to natural sunlight, 10% notice no difference, and 10% report deterioration. This observation has led to the widespread use of artificial ultraviolet radiation as one method of treating psoriasis either singly or in combination. Broad band ultraviolet B (290-320 nm) has been widely used for many years either as monotherapy or to augment the effects of topical agents such as topical tar and dithranol. Several studies of large populations of patients with psoriasis have failed to find an increased incidence of any type of cutaneous or systemic malignancy in patients with psoriasis treated in this way compared with local controls.^{1,2}

A new addition to treatment with ultraviolet B is the narrow band TLO1 lamp emitting radiation at 312 nm. This wavelength clears psoriatic plaques more rapidly than older broad band ultraviolet B sources but not enough data are available to report on the ratio of risk and benefit of this approach. Ultraviolet A or longwave artificial ultraviolet sources (320-360 nm) may benefit some patients with psoriasis who use sunbeds which are usually equipped with tubes emitting this wavelength, but for greater benefit a systemic photosensitising agent, a psoralen (PUVA), is

usually added. While PUVA is effective in clearing stubborn psoriasis it is teratogenic and full contraceptive precautions must be taken by young women. There is now also evidence that high total cumulative doses of ultraviolet A given with a psoralen photosensitiser lead to an increased incidence of squamous cell carcinoma, but not of other malignancies. The risk is greater in those who have used other carcinogenic agents as part of their treatment, such as methotrexate, but is still seen in patients who have used only PUVA.³

Traditional broad band ultraviolet B sources are safe and non-carcinogenic if used in controlled conditions for intermittent courses (commonly three exposures a week for six weeks). There are no data on the new narrow band source or on ultraviolet A used alone.

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Who should decide? Qualitative analysis of panel data from public, patients, healthcare professionals, and insurers on priorities in health care

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Abstract

Objective: To explore the arguments underlying the choices of patients, the public, general practitioners, specialists, and health insurers regarding priorities in health care.

Design: A qualitative analysis of data gathered in a series of panels. Members were asked to economise on the publicly funded healthcare budget, exemplified by 10 services.

Results: From a medical point of view, both panels of healthcare professionals thought most services were necessary. The general practitioners tried to achieve the budget cuts by limiting access to services to those most in need of them or those who cannot afford to pay for them. The specialists emphasised the possibilities of reducing costs by increasing the efficiency within services and preventing inappropriate utilisation. The patients mainly economised by limiting universal access to preventive and acute services. The "public" panels excluded services that are relatively inexpensive for individual patients. Moreover, they emphasised the individual's own responsibility for health behaviour and the costs of health care, resulting in the choice for copayments. The health insurers emphasised the importance of including services that relate to a risk only, as well as feasibility aspects.

Conclusions: There were substantial differences in the way the different groups approached the issue of what should be included in the basic package. Healthcare professionals seem to be most aware of the importance of maintaining equal access for everyone in need of health care.

Introduction

As the costs of health care continue to increase and will do so even more as our populations age the question of what services a society can afford to offer to its citizens continues to occasion debate. Recently readers of the *BMJ* were confronted with a discussion of the Swedish report on prioritising health care¹ and on Dworkin's thought experiment on creative rationing.² Central to this debate of course is the notion that there are choices to be made. Previous studies have shown that among the parties involved (public, professionals, patients), no consensus exists for these choices.³⁻⁵ This raises the question of whether the arguments used to defend the different choices are consistent.

To develop some understanding about the arguments underlying the opinions of different parties we carried out a study with panels of five parties that might be concerned in prioritising: the public and patients, health insurers, and two groups of healthcare professionals—general practitioners and medical specialists. We report on their preferences but focus on

the criteria developed to select services to be included in a basic package as well as the arguments used in specific instances.

Subjects and methods

The study took place in the Netherlands. In the Netherlands the (public) debate on prioritising health care started almost 10 years ago. Several reports on this issue have been published since then, the best known of which is the report of the Dunning committee, named after its chairman Professor Dunning.⁶ The public debate has been stimulated by the government—for example, by means of a campaign aimed at making people aware of the necessity of making choices.

In this study, six panels (box), consisting of about nine people each, were asked to play the part of a parliamentary committee with the decision to select services that would continue to be funded from a severely cut health budget. The list consisted of 10 different services, selected to represent different aspects of physical health care (table 1). The decisions to be made were restricted to those who receive public insurance, which currently covers about two thirds of the Dutch population.

The panels were given two sources of background information: the selection criteria as proposed in the Dunning report, *Choices in Health Care: Necessary Care, Effectiveness, Efficiency, Too Expensive for the Individual* (the criteria are summarised in the box on the next page)⁶; and a file on each of the services under consideration, containing information on its nature, the number of people affected (now and in the future), costs, and current restrictions. This information is summarised in table 1. In addition, they received a few papers stating the views of supporters and opponents of public funding.

The panels were asked to economise nearly one third of the total budget. They had to decide whether a

The panels

Patients:
People representing national patient groups
The public:
University students
Civil servants not working on health
(None of the members of these panels suffered from a chronic illness or handicap)
Healthcare professionals:
General practitioners, in the last stage of their training
Specialists in an academic hospital
Health insurers:
Employees working in a health insurance company

Table 1 Services included in list and summary of the information given to panel members

Service	Summary of background information given*	Costs (in million Dutch guilders)†	No of people affected
Home care	Nature of care (mostly household support, care was only small part) Age distribution of clients (mostly elderly people) Copayments Waiting lists	1740	About 7.5% of households
Circumcision for men	Reasons for circumcision (about 60% of cost for religious reasons, rest of costs: medical) Providers: general practitioner, hospital (former much cheaper), and traditional doctors	10	About 9000 circumcisions a year
Homes for the elderly	Copayments (costs of living paid by inhabitants themselves) Future demographic developments	3185	About 6% of population >65 years
Homoeopathic medicines	Effectivity (effectiveness not proved yet) Comparison with total costs of medicines (only 1% of total costs)	40	Many (exact number unknown)
Screening for breast cancer	Epidemiological data (incidence, etc) Scientific basis of current programme (cost effectiveness study; number of life years gained)	45	Women aged 50-70 years (around 400 000)
Lung transplantation	Characterisation of patients in need of transplantation Waiting lists (limited number of transplant lungs) Cost per transplantation, follow up included (about 300 000 Dutch guilders)	6	About 20 transplantations a year
Travel allowances	Nature of service (allowance of costs made in order to travel to healthcare services) Copayments Future developments (higher costs because of demographic developments, etc)	172	12% Of insured population
Oral contraceptives	Nature of service (effective, risks almost nil) Price for individual (maximum 100 guilders year)	145	About 35% of women aged 16-50 years
In vitro fertilisation	Effectivity (similar to "natural" pregnancies but more complications) Restrictions (maximum of 3 treatments publicly funded) Costs per treatment	15	About 5500 treatments a year
Treatment of sport injuries	Character of treatments (which sorts) Nature of costs: costs of medical care	280	2.7 Million accidents a year

*Selective information only; information panels received was more extensive.

†Refers to publicly funded costs (in 1993), copayments excluded (around 3 Dutch guilders=£1(\$1.6)).

certain service should be included in the basic package (that is, provided with public funds) or removed from the package, totally or partially. More importantly, they had to give arguments for each choice. They were given five hours to complete their task. One panel member led the discussion. The discussions were observed by one of the researchers and a facilitator structured proceeding as necessary. To check the unanimity of the outcomes of the discussion the panel members were asked to fill out a questionnaire afterwards concerning their private opinions. All discussions were tape recorded and transcribed verbatim.

The panels were not chosen to be a representative sample of the population but were selected on purpose. They represented five distinct parties in health policy. The individual members of the panels were selected by someone who was familiar with one of the selected parties. The main selection criteria were: interest in the subject, willingness to spend a full day on the experiment, and availability. The "patient" panel

was the only one in which the members were also formal representatives as they were all active officers of national patient associations. There were two "public" panels, one of which consisted mostly of university students, who were thus on average younger than the other panel members. Moreover, all participants were well educated, which made it possible for them to assess the information given even though they were not familiar with it.

Results

All panels fulfilled their task, although with great difficulty. It was obvious that most services could not be easily excluded from coverage in a basic package and that the budget cuts to be achieved were high. Table 2 summarises the choices made by each panel.

General practitioners

The general practitioners especially found themselves in a dilemma as they could not really envision any of the services being reduced without affecting patients in real need of them. They therefore tried to achieve cost reductions by limiting access to services, either to those most in need of them or to those who cannot afford to pay for them. For example, they discussed restricting travel allowances to low income groups and decided to pay for in vitro fertilisation only when a woman has no or only one child. In addition, they decided to restrict the universal accessibility of home care to nursing care only, but the answers to the questionnaire they filled in afterwards showed that most of the panel members felt very uncomfortable about this decision. It is remarkable that "responsibility of the individual" was not used by this panel as an argument for exclusion of services.

Dunning criteria

Publicly funded services should meet the following criteria:

- Necessary care—care which is necessary to maintain or to restore health, defined as the ability to function normally in the community
- Effectiveness—this has to be proved and documented
- Efficiency—efficient delivery, based on the results of cost effectiveness studies
- Individual responsibility—too expensive for the individual

This underlies the unanimous choice to include treatment of sport injuries in the benefit package.

Specialists

The medical specialists also thought that most of the services were necessary. Their criteria for inclusion were the most explicit: prevention or curing of a disease or caring for sick people. In their eyes infertility was a disease thus in vitro fertilisation was included in the basic package. Using that same argument, however, they went on to exclude oral contraceptives. A second argument used in that discussion emphasised that most of the cuts proposed would affect old people. The panel thought that excluding oral contraceptives was one way to spread the effect more equitably over age groups. They emphasised possible economies from increased efficiency within the existing services, such as home care and prevention of inappropriate use of travel allowances. Compared with the other panels, the specialist were more concerned about prevention and hence included breast cancer screening.

Patients

The patients made a clear distinction between those suffering from a long term or chronic illness and those with an acute disease or healthy people. They thought that especially health services for the former should be publicly funded as chronically ill people have no other option but to rely on health care. They therefore firmly rejected cutting costs of long term home care and travel allowances. On the other hand, they (partly) excluded preventive services as well as severely cut acute care (including short term home care after hospital discharge) and health care needs related to individual behaviour (such as treatment of sport injuries).

Public

Both panels representing the public looked very carefully at the argument of financial resources of the individual and individual responsibility for health. Those services that were relatively inexpensive or allowed

alternative solutions for the individual were (partly) excluded. These included travel allowance, oral contraceptives, and in vitro fertilisation. These choices reflect a high value placed on the principle of individual responsibility, which was confirmed by the answers given in the questionnaire. They proposed copayments for health care in the case of sports injuries and breast cancer screening, a decision consistent with their earlier arguments.

Health insurers

The panel of health insurers introduced two criteria specific to their occupational background. In the first place they separated health risks (for which one can be insured) and inevitable healthcare needs that will eventually be experienced by most of us (home care and homes for elderly people). They thought that the latter should be provided through taxation rather than through insurance. They also emphasised the feasibility of implementation of the measures proposed. For that reason they argued against excluding sports injuries or selecting those in real need for reimbursement of travel allowances and in favour of the total exclusion of oral contraceptives.

All panels

Despite these clearly distinct approaches to the question of priorities, there were also some similarities. All panels argued that homeopathic medicines should be excluded from public funding as their effectiveness has not been proved. They all decided to cut down the costs of the homes for elderly people, the underlying rationale being the wish to deliver services more efficiently. In addition, the panels seem to agree on the value of lifesaving services, as exemplified by lung transplantation. Yet all groups questioned the cost-benefit ratio of this service, which reflects the high value attached to efficiency.

Discussion

The panels were able to reach a consensus, although it was obvious that many of the concepts used and much

Table 2 Choices made by each panel as to whether service should be publicly funded

Service	General practitioners	Specialists	Patients	Public		
				Students	Civil servants	Health insurers
Home care	Partly: medical care only	Partly: higher copayments + cost reduction by increased efficiency	Partly: long term care only	Partly: medical care only	Yes	Partly: short term care only
Circumcision for men	Partly: medical indication only	Partly: copayments in case of religious reason	Partly: copayments in case of religious reason	No	Partly: medical indication only	No
Homes for the elderly	Yes + cost reduction by limiting access to people most in need	Yes + cost reduction by limiting access to people most in need	Yes + cost reduction by limiting access to people most in need	Yes + cost reduction by limiting access to people most in need	Partly: medical care only	No
Homeopathic medicines	No	No	No	No	No	No
Screening for breast cancer	Yes	Yes	Partly: copayments	Yes	Partly: copayments	Yes
Lung transplantation	Yes	Yes	Yes	Yes	Yes	Yes
Travel allowances	Partly: those most in need only + copayments	Yes + cost reduction by preventing inappropriate utilisation	Yes + cost reduction by preventing inappropriate utilisation	No	Partly: copayments	No
Oral contraceptives	Partly: medical indication only	No	Partly: medical indication only	No	Partly: medical indication only	No
In vitro fertilisation	Partly: access restricted + copayments	Yes	No	No	No	No
Treatment of sport injuries	Yes + reducing costs by increased efficiency	Yes	No	Partly: copayments	No	Yes

of the material offered were alien to many of the panel members. It is therefore unlikely that an exercise like this could be easily used to elicit opinions of the general public. Additional evidence to support this view is provided by a recent experiment on citizens' juries among the general public.⁷ That experiment showed that if the general public is to be involved in decisions on prioritising in health care they need much more time and information than the five hours and the written information that the participants in our study were given.

Given the fact that the panel members were relatively young and highly educated, they were far from random samples. Therefore the panels should not be considered as representing the whole population of patients, general practitioners, etc. It could be questioned whether this threatens the validity of our results. In general demographic characteristics do not seem to be systematically related to the decisions people make in prioritising processes.⁸ An exception should probably be made for age as a recent study showed that people seem to favour services for their own age group.⁵ If this is true, the panels probably would have been more reluctant with respect to cutting costs for home care and homes for the elderly if more elderly people had been included. On the other hand, a specific check on the age distribution of the proposed cuts was discussed explicitly by at least one of the panels. Moreover, our aim was to obtain more insight into the arguments underlying the choices of different actors in the decision making process, rather than into the outcome of the prioritisation process. We do not consider it likely that the arguments strongly differ by age or other characteristics.

In view of the limited share of resources that can be devoted to health care, all panels chose to exclude ineffective services from public funding and tried to deliver services more efficiently. Hence the idea of effectiveness and efficiency as necessary conditions for the general accessibility of our future healthcare system seems widely shared. This was confirmed by the data obtained by the questionnaire. In addition, all groups seemed to agree on the value of lifesaving technologies. The discrepancy with the results of other studies suggesting that the public and professionals disagree in this respect^{3,9} might be explained by the fact that we chose lung transplantation as an example of high technology, a service which mostly benefits young people. Moreover, the costs of this service represented only a small proportion of the total budget.

Observed differences

Besides these similarities we observed substantial differences in the arguments of the groups considered. Patients and health insurers in particular explicitly introduced self interest as a basis for prioritising. The patients, all suffering from a chronic illness, considered care services to be the most important, which corresponds with the results of another study regarding primary healthcare services.⁴ The choices of the health insurers were guided mainly by their concern for the practical feasibility of the chosen strategy. We found little evidence to suggest that the public or healthcare professionals were guided by personal needs or self interest, which is consistent, as

far as the public is concerned, with the results of a previous study.¹⁰

Partly because of differences in the approach to the population's best interest, but probably also because of differences in first hand experience with the people using the different services discussed, the main difference between the panels seems to be the extent to which they took the principle of equal access into consideration. This finding seems to be in accordance with that of a previous studies.^{3,11} Members of the public panel in particular frequently emphasised the importance of individual responsibility. In accordance with this principle, copayments were proposed without paying much attention to whether this might affect the accessibility of health care for low income groups. Although the outcome here may have been biased by their relatively high level of educational and income, the results of a survey among a random sample of the public³ also showed that priorities set by the general public might be contrary to the principle of equity and equal access. In addition, while focusing on a conception of health care in terms of care for the chronically ill, the strategy of the patients might threaten the accessibility for those with an acute illness or healthy people. In contrast, the healthcare professionals, and in particular the general practitioners, explicitly took into account the consequences of their decision for the equal accessibility of services. In addition, the specialists discussed the distribution of the proposed economies across age groups.

Finally, the healthcare professionals were the most pessimistic about the possibilities of cutting down public expense on health care. The strategy of not offering those services under public funding was hardly an acceptable option to them, whereas the possibilities for other strategies, such as restricting access to specific groups, was limited by the high value attached to the principle of equal access. A cynic might argue that doctors would be expected to be most reluctant to cut healthcare costs out of self interest, but the arguments used and the tone of the discussion suggest otherwise. The difficulties encountered by the healthcare professionals in the decision making seem

Key messages

- Interest in the opinions of different parties concerned with the process of prioritisation of health services is high
- This study aimed at understanding the arguments underlying the opinions of the public, patients, healthcare professionals, and insurers
- There seem to be substantial differences in the way the different parties approach the issue of what services should be collectively funded
- The main difference seems to be the extent to which the parties took the principle of equal access into consideration
- Including all the different parties in the decision making process will therefore not necessarily lead to more equitable or broadly supported outcomes

to reflect a more realistic picture of current practice in health care, as well as a greater awareness of the importance of maintaining equal access.

From our results it is not clear that including all the different actors in the decision making process of prioritisation of health services will lead to more equitable or broadly supported outcomes or to better health for the population. It is quite remarkable that it is the medical profession that seemed most concerned about the common good and the distribution of services. The panels representing the public, patients, and insurers had much more trouble weighting the interests of all those concerned. As a result, their decisions might threaten the universal accessibility of core services. As this principle is highly valued in western societies this may be unacceptable for at least professionals, as our results show, but also for policy makers. The arguments put forward by the different groups, however, are well worth considering because they clearly reflect the different perspectives of those affected by prioritisation. We think that they all deserve to be carefully considered by the (democratically elected) bodies that decide on resource allocation in most of our healthcare systems.

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Genetic linkage of mild malaria to the major histocompatibility complex in Gambian children: study of affected sibling pairs

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Case-control studies have shown that genes for the major histocompatibility complex influence the presentation and outcome of severe *Plasmodium falciparum* disease (cerebral malaria or severe anaemia).^{1,2} To assess the role of these genes in mild disease, we conducted a genetic analysis of sibling pairs concordant for this phenotype. The affected sib-pair method compares the observed and expected distribution of parental alleles at marker loci inherited identical by descent (ibd). At any locus, a pair of siblings may share 0, 1, or 2 alleles in the ratio 25%:50%:25%, by random segregation. If a locus is genetically linked to disease, affected siblings will share a higher number of alleles identical by descent at that locus than expected.

Subjects, methods, and results

We recruited 217 dizygous pairs of Gambian twins (mean age 5.3 years).³ Twins living together are important for such a study, for they are of the same age and share a common environment. They were monitored weekly during the 1991 rainy season for development of fever and *P falciparum* infection. Clinical malaria was defined as fever (axillary temperature $\geq 37.5^\circ\text{C}$) plus *P falciparum* asexual parasitaemia $\geq 5000/\mu\text{l}$. Surveillance continued through the next two rainy seasons,

producing a total of 40 pairs of twins who were concordant for clinical malaria; none had severe disease.

Major histocompatibility complex class II typing of these children and their parents was by TaqI restriction fragment length polymorphism analysis; the cDNA probes used for hybridisation were specific for DRB and for DQB. Additional typing was by fluorescence labelled microsatellite markers that map to the major histocompatibility complex region (d6s291, d6s273, tnfa, d6s276). A maximum of four individual alleles were labelled within each family. Analysis was by GAS (Genetic Analysis System, version 1.6; Alan Young, Oxford) and the MAPMAKER/SIBS program, which uses a maximum likelihood method that takes into account partially informative matings to infer sharing of alleles identical by descent at the unknown loci and thereby to compute, at each location, a maximum lod score (log 10 of the likelihood of estimated sharing divided by the likelihood of no excess sharing).⁴

Four families had moved away from the study area before the end of the study, and parents in four families had inadequate samples; in nine families one parental sample was not available, and in one family a parent was homozygous at all of the loci tested. The 22 fully

Table 1 Distribution of shared alleles mapping to the major histocompatibility complex by affected sibling pairs concordant for malaria in 22 families with complete information (based on the single most informative marker for each family)

No of pairs with malaria	No of shared alleles		
	2	1	0
Observed	11.0	10.0	1.0
Expected	5.5	11.0	5.5

informative families were analysed by the GAS program (table 1).

The MAPMAKER/SIBS program estimated the maximum likelihood values of the allele sharing proportions for each marker for 32 families (the 22 above plus the 10 families with incomplete data) to estimate the maximum lod score, which was 2.77 ($P < 0.001$) at the tnf α locus. For comparison, sharing of major histocompatibility complex alleles was not increased among 13 pairs of dizygous twins who were discordant for clinical disease (only one member of each pair having developed clinical malaria during the three year observation period) (data not shown).

Comment

The significantly non-random sharing of alleles indicates a large effect of the major histocompatibility

complex on risk of uncomplicated malaria. The linkage approach may be a more powerful means of assessing the overall influence of the complex in infectious diseases, for previous studies of uncomplicated malaria have detected no association with individual alleles.⁵ Three genes of the major histocompatibility complex are already known to affect the outcome of malaria infections; others may remain to be identified.

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A memorable patient

My only patient in general practice

I was a medical student, on my general practice placement, and my medical knowledge was confined to what a pharmacology intercalated BSc course and a year's clinical medicine had taught me. That morning, the singlehanded general practitioner's receptionist said that he was ill and asked me to come back in an hour's time. I was naive enough for this to strike me as ironic, and returned to find the receptionist and the doctor's non-medical wife looking worried. They asked me to have a look at him. I was shocked to see him heavily sedated, with pin point pupils. With a bit of shaking I roused him and discovered that he had had severe toothache the night before and had taken a couple (or was it four?) Temgesic (buprenorphine) tablets which a drug representative had left. Could he have mixed them up in his mind with Distalgescic (paracetamol)?

I was a bit concerned at his state, but equally unsure what to do. My intercalated BSc swam vaguely into consciousness. I strode to the teaching hospital which was fortuitously nearby, found the dispensary, and spoke with empty confidence to the pharmacist.

"I'm a medical student attached to Dr Jones's practice up the road. He's got a patient who has taken an overdose of opiates, and wants some intramuscular naloxone. Can I have some quickly to take back please?"

The pharmacist was unimpressed.

"I don't know about that. I'm not sure I have it to hand, and, anyway, we can't make up general practitioners' prescriptions."

Before she could refuse again I said, "Look, if this patient dies I should imagine you would be considered wholly responsible. Naloxone is hardly the sort of thing people abuse, is it?"

Perhaps the logic of the final remark impressed her, or it might have been the distant possibility of being in some way held responsible. She reluctantly gave me two vials of naloxone, with strict instructions to return with a prescription and further explanation.

I ran back with the vials and found a syringe and blue needle. Green seemed too big to be plausible, but I had no idea what you were supposed to use. I had never given any sort of injection, having previously confined my instrumentation to venepuncture. Just before I plunged the needle into his deltoid I asked, "Are you a drug user? I should say so now if you are, because I don't know if this is going to give you withdrawal symptoms serious enough to kill you."

I thought he had shaken his head. I hoped so. I hoped that intramuscular injections could not be fatal in inexperienced hands and gave him the naloxone.

He came round. I had feared that he would be angry but I was surprised to find that he seemed OK, even grateful. Both vials were eventually needed.

I never went back to the dispensary. When I finished the attachment I got a top grade and the comment that my clinical pharmacology was exemplary.

James Barrett, senior registrar in psychiatry, London

We welcome filler articles of up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.