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Prospect-EPIC Utrecht: Study design and characteristics of the cohort population

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Abstract. The European Prospective Investigation into Cancer and Nutrition (EPIC), which has been established in order to investigate the relations between nutrition and cancer, was initiated in 1990 and involves 10 European countries with heterogeneous dietary patterns and differing cancer incidence rates. This manuscript presents the design, recruitment and baseline characteristics of the Prospect-EPIC cohort co-ordinated in Utrecht, The Netherlands. The cohort is based on volunteers recruited among women participating in a regional breast cancer screening program. It comprises of 17,357 subjects aged 50–69 years at enrolment from Utrecht and vicinity, who have consented to participate in the study and its follow-up. Each participant filled out a general questionnaire and a food frequency questionnaire. Participants were also physically examined and have donated a blood sample. Participation rate was 34.5%. Blood samples were donated by most participants (97.5%) and detailed informed consents were obtained from 87.4% of participants. Mean age at enrolment was 57 years. Anthropometric, lifestyle and morbidity characteristics of the cohort population did not differ largely from those of similar study populations in The Netherlands. Based on the Prospect-EPIC population, we intend to conduct prospective total cohort, nested case–control or case–cohort studies, in order to investigate relations between consumption of certain food groups or nutrients and chronic diseases, including hormone dependant cancers such as breast, colon, endometrial and ovary cancers.

Key words: Characteristics, EPIC, Nutrition and cancer, Prospect-EPIC, Study design, The Netherlands

Background

Two decades ago it was suggested that diet might be responsible for a substantial proportion of total cancer incidence [1]. Since then, evidence has accumulated supporting the general association between dietary factors and cancer. The most consistent result so far is that a diet rich in vegetables and fruit is associated with lower risk for cancer, mostly gastrointestinal and respiratory and possibly breast cancers [2–6]. Various hypotheses have been tested in order to explain these observations. However, results of randomised studies on specific nutrients have been disappointingly inconclusive [7–14].

The idea of setting up large multi-centre prospective studies based on populations with a wide variation both in diet and in cancer incidence, in order to clarify the nature of diet-cancer associations, was conceived during the late 1980s [15, 16]. The European community, with its marked heterogeneity of exposure (i.e., different diets) and the varying incidence of certain malignancies seemed ideal for conducting such an investigation. That, in fact, was the rationale for establishing the European Prospective Investigation into Cancer and Nutrition (EPIC) [16].

The EPIC study is co-ordinated by the International Agency for Research on Cancer (IARC) in Lyon, France. EPIC was initiated in 1990, first in seven countries (France, Germany, Greece, Italy, The Netherlands, Spain and UK), and later in Denmark, Sweden and Norway [17, 18]. Data from participants in all study centres were obtained by four routes: (1) self-administered questionnaires on non-dietary variables; (2) Dietary exposure, which was approached by country-specific dietary assessment methods capable of measuring habitual food intake on the individual level on one hand, and by designing a highly standardised dietary assessment tool for calibration of dietary measurements between EPIC centres [19]; (3) Anthropometric measurements; (4) Blood samples [16]. Implementation and recruitment of the EPIC study has been completed in all participating countries by 1999. Our objective is to present the detailed design and baseline characteristics of one of the two Dutch EPIC cohorts, the Prospect-EPIC cohort co-ordinated in Utrecht, The Netherlands.

Study design and methods

The cohort study co-ordinated by the University of Utrecht is named the Prospect-EPIC study, and its population consists of women residing in Utrecht and vicinity who were invited to join the study through an existing regional population-based program of breast cancer screening, a screening program that had been established in 1974 [20].

The regional screening program became nationwide in 1990 and is based on mammography at regular intervals of 2 years [21]. All women of age cohorts over 50 are invited personally by mail to a screening centre in their residential area at a given date and time. Overall attendance rates for breast cancer screening for the total 50–69 years old female population group in The Netherlands for the years 1990–1995 were 77.5%, attendance rates for first screening round being somewhat higher (78.5%) than for second or third screening rounds (76.5 and 76.7% respectively) [21].

A pilot study ruled out the possible risk of reducing rates of breast cancer screening participation due to inviting women to the Prospect-EPIC study [22]. The study was approved by the Institutional Review Board of the University Medical Centre Utrecht.

Recruitment and data collection

From 28.6.1993 until 28.11.1997, women aged 50–69 years living in the city of Utrecht and vicinity who were scheduled for breast cancer screening during this period of time, received a mailed invitation to join the Prospect-EPIC study, along with their invitations for a routine mammography. Those who agreed to participate in the Prospect-EPIC project, subsequently received by mail two detailed questionnaires, one regarding non-dietary factors, the other a food frequency questionnaire (FFQ), referring to habitual dietary patterns. The FFQ included photographs of certain characteristic local foods and portion sizes, as well as information about intake of food supplements. The FFQ and the section concerning physical activity in the general questionnaire have been validated in pilot studies prior to the start of the study [23–25].

On the scheduled breast screening date, subsequent to their mammographic examination, participants were approached by study staff at seven different screening centres (Utrecht, Tiel, Amersfoort, Bunschoten, Leusden, Veenendaal and Zeist). An informed consent form was signed by all participants, and following an inspection of the filled-out questionnaires by the study staff, a medical examination – including measurements of pulse rate (×2), blood pressure (×2), height, sitting height, weight and waist and hip circumferences – was performed. Finally, a 30 ml non-fasting blood sample was donated by each participant, using three safety vacuum monovettes, one dry monovette for serum and two citrated monovettes for plasma. Within 24 hours, samples of 4 ml serum, 9 ml citrate plasma, 2 ml white blood cells and 2 ml red blood cells were fractionated into 0.5 ml aliquots and stored in heat-sealed plastic straws, first at −80 °C and later under liquid nitrogen at −196 °C, for future use. Half of the aliquots (14 straws per subject) was stored locally, whereas the other half was periodically transported to Lyon by road under liquid nitrogen, to be stored in the central bank of biological samples at IARC.

Filled-out questionnaires were coded and computerised.

Follow-up

Participants are followed up for vital and health status. Dates of migration or death are obtained through municipal registries. Causes of death are obtained through the general practitioners. Cancer incidence information is obtained through yearly linkage with the regional and national cancer registries.

Postal follow-up questionnaires will be sent within regular intervals (3–5 years) to all participants, in order to detect changes in exposure and in health status (i.e. incidence of cardiovascular diseases, diabetes etc.).

Analysis

Participation rates and description of baseline characteristics of the Dutch Prospect-EPIC study will be presented. All analyses were done using the SPSS 9.0 statistical package for Windows. Data concerning the food frequency questionnaires and specific dietary patterns will be the subject of a separate paper.

Results

Participation rate in Prospect-EPIC study

In total, 50,313 Dutch women were invited to take part in the EPIC study between 1993–1997. Of them, 17,357 (34.5%) agreed to take part (Table 1). Compliance was somewhat higher for the younger women and for women from less urbanised areas. Participation rates were lower in the last study year due to logistic causes (Table 2).

Selected characteristics

Most participants were between 49–59 years of age at enrolment (Table 3). Of the total cohort, 94% were born in The Netherlands. Most of the women were married (76.2%). Participants' partners were somewhat more educated than the participants themselves (Table 4).

Table 1. Participation rates according to age group, year of birth and living area

Variable	Total invited group	Participants (Percentage of those invited)
N	50,313	17,357 (34.5)
Age at invitation (years)		
49–54	19,523	7313 (37.5)
55–59	11,218	3878 (34.6)
60–64	10,137	3533 (34.9)
65–70	9435	2633 (27.9)
Mean age ± SD	57.6 ± 6.2	57.0 ± 6.0
Year of birth		
1921–1930	10,471	3093 (29.5)
1931–1940	21,610	7622 (35.3)
1941–1950	18,232	6642 (36.4)
Year of invitation		
1993	5035	2086 (41.4)
1994	12,344	4449 (36.0)
1995	13,088	4423 (33.8)
1996	11,060	4537 (41.0)
1997	8786	1862 (21.2)
Area of living		
Utrecht – city	18,750	5485 (29.3)
Utrecht county	31,563	11,872 (37.6)

Table 2. Year of enrolment

Year of enrolment	Number (Percentage of total participants)
1993	1491 (8.6)
1994	4579 (26.4)
1995	4441 (25.6)
1996	4494 (25.9)
1997	2352 (13.5)
Total	17,357 (100.0)

Table 3. Age of participants at study entry

Age at study entry (years)	Number (Percentage of total participants)
49–54	7162 (41.3)
55–59	3986 (23.0)
60–64	3483 (20.1)
65–70	2771 (15.7)
Total	17,357 (100.0)
Mean age ± SD	57.1 ± 6.0

Questionnaires and blood donations

All of the cohort participants have taken part in the study entry interview, complete data were obtained for the vast majority (Table 5). Non-fasting blood samples, successfully drawn from 97.5% of the women, were donated in the morning (08:00–10:00, 33.9%), noon time (11:00–13:00, 37.9%), or the afternoon (14:00–16:00, 28.2%). On average, participants had eaten their last meal approximately 2 hours (median: 2:12 hours, range: 0–20 hours) and had drunk their last drink approximately 2 hours (median: 2:02 hours, range: 0–15 hours) before blood donation.

Of the total cohort, 87.4% have signed a detailed informed consent, enabling the researchers to use their blood samples, contact their GP's, perform linkage with local municipalities and mortality registry as well as with the local and national cancer registries, and re-contact them in the future.

Table 4. Educational level of cohort participants and their present partners

	Cohort participants (%)	Partners of participants (%)
Primary school completed	3841 (22.1)	1621 (9.3)
Technical/ professional education	8148 (46.9)	5068 (29.2)
Secondary education	2430 (14.0)	3083 (17.8)
Academic education	2796 (16.1)	3808 (21.9)
Subtotal	17,215 (99.1)	13,580 (78.2)
Missing	142 (0.8)	404 (2.3)
No partner		3373 (19.4)
Total	17,357 (99.9)	17,357 (99.9)

Table 5. Completeness of data

Variable	Present	Not present	Missing
Intake interview	17,338 (99.9%)	19 (0.1%)	–
General questionnaire	17,235 (99.3%)	122 (0.7%)	–
Food frequency questionnaire	17,239 (99.3%)	118 (0.7%)	–
Blood withdrawal	16,929 (97.5%)	427 (2.5%)	1

Anthropometric and other measurements

Mean height and weight are presented in Table 6. Sitting height (taken on a standard 43 cm height chair) was 85.9 ± 3.7 cm. Means of the two measurements taken for pulse rate and blood pressure were calculated; mean pulse rate was 73.8 ± 11.4 per minute; mean systolic and diastolic blood pressures were 133.2 ± 20.1 and 79.3 ± 10.4 mm Hg, respectively.

Table 6. Anthropometric indices

	Height (cm)	Weight (kg)	BMI*	Waist (cm)	Hip (cm)	Waist/hip ratio
Mean ± SD	164.3 ± 6.1	70.2 ± 11.5	26.0 ± 4.1	83.7 ± 10.2	105.7 ± 8.4	0.8 ± 0.1
Median	164.0	69.0	25.0	82.0	105.0	0.8
Minimum	140.0	40.0	14.0	52.0	76.0	0.6
Maximum	190.0	130.0	52.0	140.0	152.0	1.1
Percentiles						
25th	160.0	62.0	23.0	76.0	100.0	0.7
50th	164.0	69.0	25.0	82.0	105.0	0.8
75th	168.5	76.5	28.0	90.0	110.0	0.8
Missing data (N)	22	18	22	28	30	34

Smoking

Around 43% of the cohort subjects had never smoked cigarettes. A small fraction of women (6.9%) reported having smoked pipe or cigars, currently or in the past (Table 7).

Table 7. Smoking and passive smoking

Smoking variable	N (%)
Pipe or cigars	
1. Never smokers	15,947 (91.9)
2. Ever smokers	1200 (6.9)
Past	880 (5.1)
Current	320 (1.8)
3. Unknown	88 (0.5)
Cigarettes	
1. Never smokers	7466 (43.0)
2. Ever smokers	9765 (56.3)
Past (Pack years)	5982 (34.5)
<1	768 (12.8)
1–9	2868 (47.9)
10–19	1214 (20.3)
20+	688 (11.4)
Missing	450 (7.5)
Mean ± SD/median	2.8 ± 1.9 / 2.0
Current (Pack years)	3783 (21.8)
<1	44 (1.2)
1–9	908 (24.0)
10–19	1384 (36.6)
20+	1389 (36.7)
Missing	58 (1.5)
Mean ± SD/median	3.2 ± 1.0/3.0
3. Missing	126 (0.7)
Passive smoking (for never cigarettes-smokers only)	
1. Past	5775 (77.3)
By father	5221 (69.9)
By mother	100 (1.3)
By both	454 (6.1)
2. Current	7411 (99.3)
Daily	1905 (25.5)
Occasionally	5506 (73.7)

Reproductive indices

Mean age at menarche in our cohort was 13.4 ± 1.7 years; 25% of the women were younger than 12 years while 25% were older than 14 at menarche. Most of the participants (88.4%) were pregnant at least once during their lifetime, and of them 98.5% gave birth to a living baby. Mean age at first delivery was 25.1 ± 4.0 years (range: 12–44 years) and median number of children was 2 (range: 1–15). Having had at least one spontaneous abortion was reported by 23%, while 5.2% had experienced at least one induced abortion.

One-fifth of the total cohort reported to still be premenopausal at enrolment. Of those who reported being postmenopausal, 696 (4%) still had between 1 and 16 periods (median: 2) in the last twelve months. Applying the criteria of no menstrual bleeding for at least 12 months, a total of 13,018 (75.0%) women were postmenopausal, of them 51.5% underwent natural menopause, while 23.5% had an induced menopause due to surgical causes. Mean menopause age was 47.0 ± 6.0 years (median: 48.0).

Oral contraceptives were ever used by approximately 64% of the total cohort, while IUD was formerly used by 11% and currently used by 1% of the total cohort. A quarter of all participants reported ever having used hormonal replacement therapy (HRT).

Self-reported morbidity at entry

Women were asked to report all malignant diseases diagnosed prior to enrolment. A total of 6.3% reported having prevalent cancers, breast cancer being the most frequent one. Of them, 89 (8.1%) also reported a second primary tumour (Table 8). A small fraction of the cohort reported having had a myocardial infarction or a stroke. Hypertension was defined for 28.0% of the cohort participants. Of the 524 self-report diabetics, 13% were treated by diet only, 25% were treated by oral tablets, 16% were treated

Table 8. Prevalence of self-reported morbidity at study entry

Cancer morbidity (1st primary)	N (%)
Breast cancer	235 (21.4)
Cervical cancer	261 (23.8)
Endometrial cancer	81 (7.4)
Ovary cancer	23 (2.1)
Colon cancer	66 (6.0)
Lung cancer	3 (0.3)
Other	428 (39.0)
Total	1097 (100)
CVD morbidity	
Myocardial infarction	287 (1.7)
Hypertension*	4861 (28.0)
CVA	
	285 (1.6)
Diabetes mellitus	524 (3.0)

*As defined by the WHO criteria, i.e., either being treated for the disease by anti-hypertension drugs, or having a diastolic blood pressure of 95 mm Hg or higher, or having a systolic blood pressure of 160 mm Hg or higher, or any combination of these factors.

by insulin and the rest were treated by combination therapy (33%) or not treated at all (12%).

Discussion

The Dutch Prospect-EPIC cohort participants were recruited through an existing national program for breast cancer screening. This presents several advantages: first, screening centres in The Netherlands are in possession of an updated database of names and addresses of the eligible female population received from the municipal administration. Second, participants can be contacted directly as they approach the screening unit for a mammography. Third, the follow-up is easier since participants are invited periodically for a screening re-examination [22]. And fourth, when studying breast cancer prospectively, a negative screening mammography assures the disease-free state of a participant at enrolment. In addition, using a national breast screening program based on periodic mammograms as a basis for a prospective study aimed at identifying risk factors for the occurrence of breast cancer, also enables the study of mammographic changes prior to diagnosis of the disease.

The response rate in the Prospect study is similar to the rate reported in another large Dutch cohort study, in which 340,439 men and women selected randomly from the general population were invited by mail to take part. Their compliance rate was 36.6% in women, and similarly higher in younger age groups and in less urbanised areas [26].

Comparing the general characteristics of the Prospect study population to the general population is not easy, as such data are not readily available. However, some of the Prospect-EPIC cohort's anthropometric results resembled those found in the British EPIC cohort (participants' age: 45–75 years): mean BMI was 26.0 and between 25.7 and 26.7 in the Dutch and British cohorts, respectively, and means of waist-hip circumference were both 0.8 [27].

In total, 17.5% of the Prospect population were obese (BMI = 30 or higher) while in another Dutch cohort study of women older than 55 years (The Rotterdam Study), obesity prevalence was 16.8% [28].

Current smoking was reported by 22% of the cohort participants. The smoking prevalence was somewhat lower in the age group of 55 years old and over – 18.4% – and in accordance with the prevalence of current smoking among women of 55+ years of age in the Rotterdam Study (18%) [29]. Likewise, current smoking within the 55–74 years old female participants in the British EPIC-Norfolk study was self-reported by18.5% of the participants [27].

Cancer morbidity (first primary tumour) was reported by 1097 women, most of the cases attributed to breast and cervical cancers. This figure corresponds to a point prevalence of 6.3 cancer cases per 100,000 women. Point prevalence of total cancers in the total Dutch female population was 1.9 per 100,000 according to the Dutch Cancer Registry report on 1.1.1993 [30]. Our estimate is probably larger because of the older age groups included. In addition, misclassification of cancer by self-report is a plausible possibility [31]. Furthermore, screening programs may preferentially include participants with prevalent cancer because women may be eager to prevent a second cancer.

Hypertension was prevalent in around 28% of Prospect participants, of them 30% were in the age group 49–54; 22%, in the age group 55–59 (23% in the Rotterdam study); 25%, in the age group 60–64 (32% in the Rotterdam study); and 23% in the age group 65–70 (38% in the Rotterdam study) [32].

Prevalence of stroke in our total cohort was 1.6%, while in the Rotterdam study it corresponded to 2.6% [33]. Prevalence of diabetes was 3.0% in total, or 1.9, 2.6, 4.3 and 4.9% for the age groups 49–54, 55–59, 60–64 and 65–70, respectively. In the Rotterdam and the Hoorn studies, prevalence of diabetes was approximately three-fold higher (10.9% and 8.3%, respectively) [28, 34]. Different methods of diabetes assessment probably account for the difference: self-report in the Prospect cohort; plasma glucose levels and oral glucose tolerance tests in the other cohorts.

Volunteers for epidemiological research are often described as a unique group characterised by a higher proportion of women, higher education level, lower use of health services and lower mortality rates, in

comparison to non-volunteers [35–37]. The healthy volunteer effect may, therefore, call for a cautious interpretation of results in descriptive studies, especially when extrapolated to the general population. However, it is less of a problem in prospective studies aimed at investigating causal relations between baseline determinants and the subsequent development of health outcomes.

We will be using a variety of study designs in this cohort, i.e., a nested case–control study design, a case–cohort approach or a full cohort analysis [38]. Associations between certain dietary and non-dietary factors, and several chronic diseases, including hormone-related cancers, are planned to be studied in our database. In addition, we will be able to compare Dutch dietary patterns and consumption of certain food groups to those of other European countries which also take part in the EPIC project. It is our belief and hope, that such information will shed some more light on the relationship between dietary factors and cancer or other chronic diseases.

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