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The Influence of Age on Treatment Choice and Survival of Elderly Breast Cancer Patients in South-eastern Netherlands: A Population-based Study

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The influence of age on treatment choice and survival was studied in 2268 breast cancer patients of 55 years and older reported to the Eindhoven Cancer Registry from 1975 to 1987. Among patients of 75 years and older, stage I and II tumours occurred less often, whereas stage IIIb and undefined tumours occurred more often than among younger patients. Physicians were found to be less likely to treat women of 75 years and older with adjuvant radiotherapy after a mastectomy. Instead, these women received either surgery alone or surgery followed by hormonal therapy. Surgical procedures in the oldest age group were also less extensive. The 10-year relative survival for women over 74 years (32%) was significantly worse than that for younger patients (57%). Multivariate analyses showed that this poor outcome for the oldest age group was largely related to their unfavourable stage distribution: stage-specific survival appeared to be similar in all age groups. Age-related differences in treatment did not have an effect on survival.

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INTRODUCTION

IN THE Netherlands, about 45% of breast cancer patients are older than 60 years and this percentage will increase due to the growing number of elderly people in the population [1].

Despite this development the optimal treatment for elderly breast cancer patients has not been examined extensively. Treatment for elderly breast cancer patients may be less intensive, because breast cancer in this age group is considered by some clinicians to have a lower malignancy grade than in younger patients [2]. Elderly patients are also presumed not to be able to withstand vigorous treatment. The latter argument is often used to exclude elderly patients from chemotherapy trials. Another reason for an upper age limit of 65 years in most clinical trials, is the long follow-up period needed to fully evaluate possible gains in disease-free or overall survival. Elderly patients are less likely to reach the endpoint of such trials due to their higher risk of dying from comorbid diseases.

Several reports have confirmed that elderly cancer patients are less likely to receive standard treatment than younger patients [3–11]. Greenfield [5] showed that both healthy elderly breast cancer patients and patients with comorbid diseases received non-standard treatment more often than younger patients, while Mor [10] and Bergman [11] concluded that chronological age rather than comorbidity appeared to influence primary treatment choice.

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Our cancer hospital-based study also demonstrated a worse disease-specific survival for patients over 74 years compared with patients of 65–74 years, independent of the comorbidity.

In the present report, the population-based data from 10 community hospitals was used to examine treatment pattern and survival of elderly breast cancer patients in a general population.

PATIENTS AND METHODS

Data collection

Data were obtained from the population-based Eindhoven Cancer Registry, which serves a population of 830,000 inhabitants in the south-eastern part of the Netherlands (7% of the Dutch population). Computerised data have been available since 1975 [12]. Data were collected directly from the medical records of 10 community hospitals. Vital statistics up to 31 December 1987 were systematically checked in the municipal population registries. Less than 1% was lost to follow-up. Until 1984, only the initial treatment given within the first 6 months after diagnosis was documented in the registry. Since 1984, the Regional Breast Cancer Study Group initiated the collection of additional data on clinical stage, type of surgical/radiation treatment, and dosages of hormones and chemotherapy. For quality checks, treatment data gathered by the registry after 1983 were compared with treatment data on the same patients collected on behalf of the Regional Breast Cancer Study Group. Primary treatment documentation was found to be complete in 97% of the cases.

All breast cancer patients of 55 years and older at diagnosis and treated between 1 January 1975 through to 31 December 1987 were eligible for the study (n = 2680). Patients with previous malignancies were excluded, as were patients with concomitant (within 1 year after diagnosis) new malignancies other than basal cell carcinoma of the skin and *in situ* carcinoma of the cervix, and patients with an autopsy diagnosis. Patients developing second primary malignancies more than a year after the primary breast tumour, took part in the study until the occurrence of the second malignancy. The study group finally included 2268 patients, who were divided into the following age groups: 55–64 years, 65–74 years and 75 years and older. Elderly women are defined as those of 65 years and older.

Therapy

Whether patterns of care varied as a function of age was examined. The Regional Breast Cancer Study Group composed and regularly adapted a manual with guidelines for cancer treatment since 1981. No special treatment guidelines have ever been given with respect to age. Patients with tumours less than or equal to 3 cm should receive either breast conserving treatment or a modified radical mastectomy followed by adjuvant radiotherapy on the parasternal field in cases of centrally or medially localized tumours [13]. For patients with tumours larger than 3 cm, a mastectomy was recommended. Postoperative radiotherapy included thoracic wall, sub- and supraclavicular regions and the axilla in all patients with positive axillary lymph nodes. Since 1980, adjuvant hormonal therapy has been introduced for patients with positive axillary lymph nodes. Patients with distant metastases at diagnosis received hormonal treatment or chemotherapy.

In order to examine whether the use of radiotherapy varied with the distance of the patient's home to the only radiotherapy department, the registration area was divided into three subareas (≤15 km, 15–30 km and ≤60 km from Eindhoven).

Statistics

Pearson's χ^2 test was used to estimate the relationship between treatment choice, age and distance to the radiotherapy department. Survival analysis was restricted to patients diagnosed between 1975 and 1985 ($n = 1950$). Actuarial curves of observed survival were compared by the log-rank test. Relative survival rates (RSR) were computed with a program from the Finnish Cancer Registry [14, 15]. The RSR is defined as the ratio of the observed survival rate of the patient group, to the expected survival rate in a general population similar except for the cancer under study (sex, age, calendar time of observation). Regional mortality rates were supplied by the Netherlands Central Bureau of Statistics.

Multivariate analyses were carried out to estimate the effect of age on observed and relative survival, simultaneously controlling for other prognostic factors. The Cox proportional hazards model was used and the statistical package 'generalised linear interactive modelling' (GLIM) [16, 17, 18]. The GLIM program calculates the proportional hazards for two survival periods separately (i.e. years 1–5 and 6–10). The following patient and tumour characteristics were entered into the models: age group, axillary nodel status, postoperative stage and treatment modality. The postsurgical stage was used (P-stage), because information on the clinical stage (C-stage) was not available until 1984. For this reason, only patients treated with surgery could be included ($n = 1429$).

Treatment with surgery alone was the reference treatment group. All other patients were treated with either adjuvant radiotherapy, adjuvant chemotherapy/hormonal therapy (CT/HT) or a combination of adjuvant radiotherapy and CT/HT. The possibly additional effect on survival for patients receiving a combination of adjuvant radiotherapy (RT) + CT/HT as compared with patients who received a single adjuvant treatment was calculated by using an interaction term. This interaction term examined the interaction between adjuvant radiotherapy and adjuvant CT/HT. A number of other interaction terms have been used of which only those with an independent and significant effect on survival were reported.

The other reference groups were aged between 55 and 65, P-stage I and axillary nodal status negative. Variables having the weakest association ($P \geq 0.05$) with the length of survival were excluded from the model by backward stepwise regression.

Table 1. Clinical stage (C stage) according to age group (≥1984)*

C Stage	Age group (years) 55–64 (n = 298)	65–74 (n = 245)	75+ (n = 192)	Total (n = 735)
I	75(25.2)	56(22.9)	32(16.7)	163(22.2)
II	103(34.6)	104(42.5)	54(28.1)	261(35.5)
IIIA	13 (4.4)	6 (2.4)	7 (3.6)	26 (3.5)
IIIB	47(15.8)	41(16.7)	50(26.0)	138(18.8)
IV	35(11.7)	18 (7.3)	14 (7.3)	67 (9.1)
Unknown	25 (8.4)	20 (8.2)	35(18.2)	80(10.9)

*No. (%)

RESULTS

The diagnosis of breast cancer was confirmed by histology, cytology or by a clinical diagnosis in 95.8, 1.5 and 2.7% of the 2268 patients, respectively. The percentage of patients with a cytological or clinical diagnosis was three times higher in the oldest age group (5%) than in younger patients.

Information on clinical stage was only available since 1984. Among patients of 75 years and older, clinical TNM stage I and II tumours occurred less often and stage IIIB tumours occurred more often than among younger patients ($P \leq 0.01$, Table 1). The clinical stage was twice as frequently unknown in the oldest age group (18%) than in younger patients (8%).

Patients of 75 years and older appeared to have postoperative stages I and II less often than younger patients (46.6 vs. 60%), while no age differences were found in higher stages ($P \leq 0.01$, Table 2). However, information on postoperative stage was not

Table 2. Postoperative stage (P stage) according to age group for surgically treated patients*

P Stage	Age group (years) 55–64	65–74	75+	Total
(1975–1987)	(n = 843)	(n = 742)	(n = 449)	(n = 2034)
I	188(22.3)	172(23.2)	83(18.5)	443(21.8)
II	309(36.7)	252(34.0)	126(28.1)	687(33.8)
IIIA	51 (6.0)	31 (4.2)	15 (3.3)	97 (4.8)
IIIB	156(18.5)	145(19.5)	87(19.4)	388(19.1)
IV	55 (6.5)	41 (5.5)	27 (6.0)	123 (6.0)
Unknown	84(10.0)	101(13.6)	111(24.7)	296(14.6)
(≥1984)	(n = 275)	(n = 228)	(n = 156)	(n = 659)
I	85(30.9)	65(28.5)	39(25.0)	189(28.7)
II	112(40.7)	105(46.1)	44(28.2)	261(39.6)
IIIA	11 (4.0)	9 (3.9)	4 (2.6)	24(3.6)
IIIB	42(15.3)	36(15.8)	32(20.5)	110(16.7)
IV	18 (6.5)	7 (3.1)	9 (5.8)	34 (5.2)
Unknown	7 (2.5)	6 (2.6)	28(17.9)	41 (6.2)

*No. (%)

Table 3. Primary treatment according to age group* (1975–1987)

Treatment	Age group (years) 55–64 (*n* = 909)	65–74 (*n* = 808)	75+ (*n* = 551)	Total (*n* = 2268)
No treatment†	9 (1.0)	16 (2.0)	24 (4.4)	49 (2.2)
Surgery (with or without CT/HT)	213(23.4)	248(30.7)	268(48.6)	729(32.1)
Radiotherapy (with or without CT/HT)	46 (5.1)	38 (4.7)	45 (8.1)	129 (5.7)
Surgery + RT (with or without CT/HT)	630(69.3)	494(61.2)	181(32.9)	1305(57.5)
CT/HT	11 (1.2)	12 (1.5)	33 (6.0)	56 (2.5)

No. (%).
*CT = chemotherapy, HT = hormonal therapy, RT = radiotherapy.
†Including patients with unknown therapy.

available in 25% of women above 74 years compared to 12% in younger patients. To determine whether the age–stage relationship might disappear when the percentage of patients with an unknown stage would be smaller, patients diagnosed since 1984 were studied (Table 2). Unfortunately, the percentage of patients with an unknown postoperative stage in the oldest age group was still relatively high (17.9%). The relationship between age and postoperative stage also remained significant ($P \leq 0.01$): elderly women above 74 years had stage I and II less often and locally advanced disease more often than younger patients. In all age groups, the percentage of patients with early disease was higher than before 1984.

The axillary lymph nodes of surgically treated patients over 75 years were less often tumour positive than in younger patients. On the other hand, this information was more often not available (22%) in the oldest age group than in younger patients (8%) (not tabled).

Primary treatment showed that 92% of patients younger than 75 years and 81% of older patients received surgery (Table 3). Surgery followed by radiotherapy was given to 65% of patients younger than 75 years and to only 33% of older patients. Instead, the latter group was often treated by either surgery alone or surgery followed by hormones (49%).

In none of the age groups was the use of adjuvant radiotherapy associated with the distance of the patient's home to the radiotherapy department (not tabled).

The type of surgical treatment has only been documented since 1984 (Table 4). Patients of 75 years and older in all clinical stages received less extensive surgery (lumpectomy/ablation/wedge resection; all without axillary dissection) more often (38%) than younger patients (5%). A modified radical mastectomy was most frequently applied in all age groups. Elderly women of 75 years and older did undergo breast conserving treatment, but the frequency diminished with age [19]. Adjuvant chemotherapy following surgery was given to only 6 (0.9%) patients, all of whom were younger than 75 years.

Treatment policy has changed over time (Fig. 1). In the late 1970s, approximately 85% of patients in all age groups were treated by either surgery alone or by a combination of surgery and radiotherapy. From 1980 onwards, adjuvant hormonal therapy following surgery has been administered to women with metastases in the axillary lymph nodes. By 1986, 35% of women with breast cancer in all age groups received adjuvant hormonal therapy.

The 10-year observed survival was approximately 50% for the 55–64 year age group, 40% for the 65–74 year age group and 12% for the oldest group (Mantel Cox $P \leq 0.05$) (Fig. 2). 5-year relative survival did not show significant differences per age group (Fig. 3). The 10-year relative survival, however, was significantly worse for the oldest group (33%, S.E. = 0.15) than for patients younger than 75 years (55%, S.E. = 0.05; $P \leq 0.05$).

In multivariate analyses, age above 74 years had an independent and significant negative effect on observed survival [β = 0.81, S.E. = 0.15, relative risk (RR) = 2.25, 95% CL = 1.66, 3.06, model not shown]. In the model with the relative survival rates, age *per se* did not have an independent prognostic effect on survival (Table 5). The stage of disease and the axillary nodal status proved to be the most important predictors of the risk of dying from breast cancer. Survival of patients receiving adjuvant radiotherapy was not influenced by the addition of adjuvant CT/HT. Conversely, the addition of adjuvant radiotherapy did not affect survival outcome for patients treated with adjuvant CT/HT. The effect on survival for patients receiving adjuvant RT plus CT/HT (n = 102) is approximated by the addition of the βs (β = 2.37) of the single adjuvant treatment groups. The exclusion of the treatment variables from the model did not influence age-related survival, indicating that the differences in treatment between age groups did not affect survival.

DISCUSSION

In community hospitals in the south-east of The Netherlands, breast cancer patients of 75 years and older were treated by adjuvant radiotherapy less often than younger patients. Instead,

Table 4. Primary therapy of surgically treated patients according to age group and clinical stage (≥1984)

Treatment	Stage I–IIIA 55–64 (*n* = 191)	65–74 (*n* = 164)	75+ (*n* = 85)	Stage IIIB/IV 55–64 (*n* = 84)	65–74 (*n* = 64)	75+ (*n* = 71)
Limited surgery* (with or without RT, CT or HT)	3 (1.6)	5 (3.0)	25 (29.4)	9 (10.7)	5 (7.8)	34 (47.9)
Mastectomy (with or without HT)	42 (22.0)	52 (31.7)	26 (30.6)	12 (14.3)	11 (17.2)	15 (21.1)
Breast conserving (with or without RT or CT/HT)	60 (31.4)	35 (21.3)	12 (14.1)	14 (16.7)	5 (7.8)	4 (5.6)
Mastectomy + RT (with or without CT/HT)	85 (44.5)	69 (42.1)	21 (24.7)	48 (57.1)	43 (67.2)	15 (21.1)
Type of surgery unknown	1 (0.5)	3 (1.8)	1 (1.2)	1 (1.2)	0 (0.0)	3 (4.2)

No. (%).
*Limited surgery: lumpectomy/ablatio/wedge resection/quadrantectomy (all without axillary dissection).

Table 5. Prognostic factors influencing relative survival for surgically treated patients (n = 1429)

Factor	Follow-up year 1–5 β	Follow-up year 1–5 S.E.	Follow-up year 6–10 β	Follow-up year 6–10 S.E.
P-Stage				
I (n = 357)	0		0	
II (n = 574)	−0.07	0.92	1.23	1.19
III (n = 412)	0.67	0.84	2.43*	1.14
IV (n = 86)	2.85*	0.80	3.90*	1.25
Treatment				
Surgery only (n = 375)	0		0	
Surgery + RT (n = 911)	−0.33*	0.15	‡	
Surgery + CT/HT (n = 41)	2.72*	0.71	1.21*	0.33
Age (years)				
55–64 (n = 629)	0		0	
65–74 (n = 529)	−0.03	0.13	−0.38	0.29
75+ (n = 271)	0.02	0.19	−0.03	0.46
Axillary lymph nodes				
Negative (n = 812)	0		0	
Positive (n = 617)	2.47*	0.46	‡	
Interaction term CT/HT. axilla (+)†	−1.40*	0.38	‡	

P-Stage = postoperative stage, CT = chemotherapy, HT = hormonal therapy.
*$P < 0.05$.
†CT/HT. axilla (+) = an interaction term between treatment by adjuvant CT/HT and a positive axillary nodal status.
‡Excluded from the model.

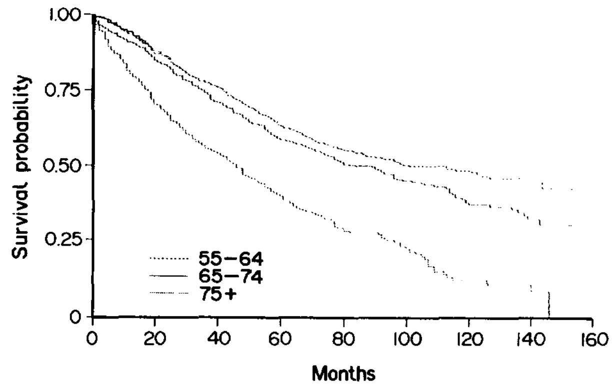

Fig. 2. Observed survival by age group.

the oldest age group received surgery alone or surgery followed by adjuvant hormonal therapy. Surgical procedures in this group were also less extensive than in younger patients.

Patients of 75 years and older presented less often with stage I and II tumours and more often with stage IIIB tumours than younger patients. This result is supported by earlier studies [20, 21], but is in contrast with recent reports, which showed no relation between age and stage [4, 5, 6, 11]. The high percentage of patients with an unknown stage in the oldest age group in this study complicates a definitive conclusion about the age–stage relationship. Several other studies [7, 11, 21, 25] have also demonstrated this increase. Possible explanations are the rise with advancing age of (a) non-surgical treatment, (b) a less extensive staging procedure or (c) a less careful documentation. Our study suggests that all these three factors played a role. Even among surgically treated patients, the proportion of patients with a well-documented stage is much lower in the oldest age group compared with younger patients.

The age–stage relationship also indicates a trend towards earlier diagnosis in all age groups over time, suggesting an increased awareness of disease symptoms and an earlier consumption of diagnostic facilities. Elderly patients, however, apparently profit to a lesser extent from these developments, probably because patient delay is still more likely in the oldest age group [22]. Although one might expect that the less extensive axillary dissection procedures in the late seventies would result in a higher proportion of patients with early stages—especially in the oldest group—(stage misclassification) [23] than after 1983, this effect could not be demonstrated in our study.

The age-related differences in treatment cannot be explained by the observed age–stage relationship. Although stage I and II tumours were observed less frequently in women over 74 years than in younger women, the elderly patients received surgery as the only treatment more often. Similarly, patients over 74 years had locally advanced tumours more often than younger ones, while they were treated less frequently with adjuvant radiotherapy. Furthermore, the increase of limited surgery with age could not be attributed entirely to a greater frequency of locally advanced tumours in the oldest age group; these procedures were also more often used in elderly patients over 74 years with early disease.

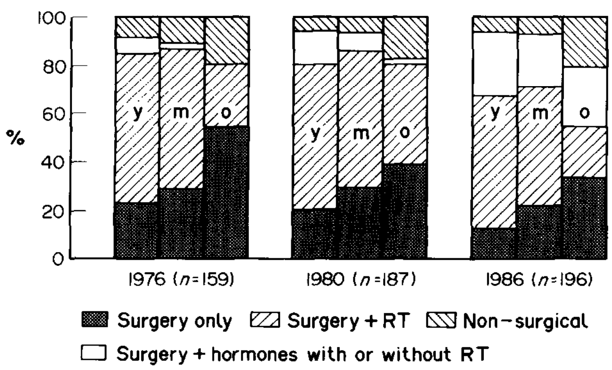

Fig. 1. Treatment according to year of diagnosis and age group. RT = radiotherapy, Y = 55–64 years, M = 65–74 years, O = 75+ years.

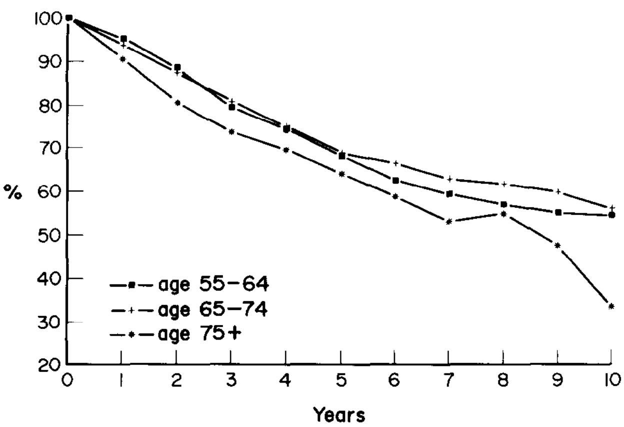

Fig. 3. Relative survival by age group.

Apart from age–stage differences, two other arguments have been forwarded to explain why elderly breast cancer patients may receive a different treatment than younger patients: age *per se* and the physical condition [4, 5, 10, 11]. Age *per se* is likely to have played a role, because women of 75 years and older underwent limited surgery without an axillary dissection more often, while a mastectomy is not considered to cause a much higher surgical risk [24]. The physical condition may have attributed to the decision against the use of adjuvant radiotherapy. Several weeks of daily travelling to the radiotherapy department can make great demands on the patient's physical condition, although the distance to the radiotherapy department *per se* was not found to affect the use of radiotherapy.

While our study did not demonstrate significant age-related differences in 5-year relative survival rates, other population-based studies have shown a worse 5-year relative survival for the elderly [7, 25, 26, 27]. However, a closer examination of these results revealed that the differences per age group were relatively small [74, 76 and 72% (SEER) and 65, 68 and 60% [26] for patients of 55–64, 65–74 and 75+ years of age respectively; 65 and 59% [25] for patients of 50–74 and 75+ years].

The 10-year relative survival of our oldest age group, however, was significantly worse than that of younger patients. The relatively low number of patients with early or regional disease (TNM I-II) and the high number with locally advanced disease in the oldest age group probably contributed to their poorer survival. Indeed, survival differences between age groups disappeared when controlling for stage in multivariate analysis. The observed age-related differences in treatment were not found to influence relative survival. This is not surprising. Adjuvant radiotherapy is intended to prolong disease-free survival, and thus the decision against this therapy would not be expected to influence disease-specific survival [28]. Furthermore, the possible negative effect of limited surgery on relative survival in patients over 74 years with early or regional disease could not be demonstrated, because the numbers were probably too small. Our earlier cancer hospital-based studies showed that disease-specific 5-year survival was significantly worse for patients of 75 years and older than for younger patients [11, 30]. Differences in the composition of the populations or in the methods used to calculate disease-specific survival may account for these conflicting results.

The treatment of the oldest group in this study does not necessarily indicate improper care. Adjuvant radiotherapy may have been omitted in favour of adjuvant hormonal therapy, which has now been shown to be effective particularly in elderly patients [29]. A second rationale for a less intensive treatment may be that it would be more appropriate for the individual patient with a compromised physical condition. The similar survival of younger and older patients is not a plea for a less intensive treatment in elderly patients: they might have had a better survival than younger patients, when they would have received standard treatment.

Unfortunately, population-based registries do not routinely collect information on treatment motives, physical condition, and comorbidity. Therefore, the effects of these factors on treatment choice and survival cannot be compared with those found in our previous study [11]. A great advantage of this study is, however, that it provides good reference information about the patterns of care and survival of a large general population.

In conclusion, this study shows that patients of 75 years and older were treated differently from younger patients. The different treatment does not necessarily indicate improper care, but a definite conclusion is complicated by the lack of data on treatment motives. Treatment differences could not be explained by the observed age-related differences in stage, but are more likely to be associated with factors such as age and comorbidity. After adjustment for stage, survival was similar in all age groups.

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Coffee Consumption and Bladder Cancer Risk

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The relation between consumption of regular and decaffeinated coffee and other methylxanthine-containing beverages and bladder cancer was analysed in a case-control study in two different areas of northern Italy (555 cases and 855 controls). The multivariate relative risk (RR) adjusted for smoking, occupation and sociodemographic variables for coffee drinkers versus non-drinkers was 1.3 (95% CI 1.0–1.8). The RR was 1.2 for one cup of coffee per day, 1.4 for two, 1.5 for three and 1.4 for four or more ($P = 0.05$). RRs for current drinkers were 1.5 (0.9–2.4) for decaffeinated coffee, 0.9 (0.6–1.2) for tea, and 0.6 (0.3–1.4) for cola. With reference to duration of consumption of coffee, RRs were 1.2 for less than 30 years or 1.4 for 30 years or more. Coffee-related RRs were higher in the older age group and in ex-smokers. Among 105 cases and 338 controls who had never smoked, RRs were 1.9 for one or two cups per day, 1.8 for three and 1.5 for four or more (trend not significant). A higher prevalence of coffee drinking among bladder cancer cases than controls was confirmed, with no clear dose–risk relation.
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INTRODUCTION

OVER THE past 2 decades, more than 30 case–control studies of coffee and bladder cancer have been published, but the issue is still open to debate [1]. Compared with non-users of coffee, in fact, the relative risks (RRs) tend to be elevated in drinkers, but such increase is not consistently related to dose or duration. This suggests that the apparent association, although present in various studies, is possibly not causal, but at least partially due to some residual confounding. Smoking is the most likely confounding factor, but the differences between crude and adjusted RRs vary from one study to another, and misclassification of smoking or insufficient adjustment for it are unlikely to explain the results from all the studies. Internal inconsistencies have also emerged in some studies, especially as regards potentially different effects of coffee according to sex [2–4] and to smoking habits [5].

Epidemiological data are much more scanty for tea and cola-containing beverages, and further information on them would be important both for the widespread use of these beverages worldwide, and the additional information they could provide on methylxanthines, which are the major common constituent.

To further investigate this issue we present here the data from a study conducted in two different areas of northern Italy. Interest of this report may lie in providing additional information useful in order to better understand the potential modifying effect or interaction of smoking or other covariates on the relationship between coffee and bladder cancer.

SUBJECTS AND METHODS

Since 1985 we have been conducting a case–control study of urological cancers in the greater Milan area and in the province of Pordenone, north-eastern Italy. The general design of this investigation has been described elsewhere [6].

Cases and controls were directly interviewed by specially trained interviewers; less than 3% of subjects approached (cases and controls) refused to answer. The structured questionnaire included a series of socio-demographic questions, detailed information on smoking habits, frequency of consumption of alcoholic beverages and of a few selected foods, history of

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