those hospitals in Great Britain where endoscopy is freely available. The procedure often facilitates an earlier decision on surgery and enables unnecessary laparotomy to be avoided. There can be few diagnostic techniques for which such strong claims could be made.

Costings of endoscopy and laparotomy were provided by Mr R Hull, Sheffield Area Health Authority Treasurer's Department.

Requests for reprints should be sent to Dr R A Dixon.

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Carcinoembryonic antigen in breast-cancer tissue: a useful prognostic indicator

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Summary and conclusions

Sections of breast carcinomas removed from 69 patients six to 13 years previously were examined using an immunoperoxidase technique to determine whether carcinoembryonic antigen (CEA) was present. Patients who had CEA-negative tumours had significantly higher five- and 10-year survival rates. The difference was not related to the stage of the disease, postoperative treatment, or histological type of tumour.

These results suggest that immunohistological assessment of CEA in breast-cancer tissue may provide more precise prognostic information.

Introduction

Recently[1] we found a positive correlation between the presence of carcinoembryonic antigen (CEA) in sections of breast carcinomas and the presence of lymph-node metastases. This further study was carried out retrospectively on a group of patients who had been followed up for six to 13 years after the surgical removal of their tumours.

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Patients and methods

We included in the study 69 patients who presented at the Royal Free Hospital during 1965-72 with breast carcinoma and were treated by mastectomy. Patients who were lost to follow-up or were known to have died from causes not related to the tumour were excluded. The first 55 patients were chosen randomly. We later included 14 consecutive patients without evidence of metastatic disease at the time of mastectomy to permit useful statistical comparison between patients in the same, early, stage of the disease.

Stored histological sections prepared from the mastectomy specimens and stained with haematoxylin and eosin were examined in all cases. Extra sections, 4 μm thick, were then cut in each case from one of the stored paraffin blocks that contained representative tissue of the primary tumour. These sections were stained for CEA using an immunoperoxidase method.[1] This entails reducing endogenous peroxidase by applying 0·5% solution of 30% hydrogen peroxide in methanol and reducing background staining by using 1:5 normal swine serum. The sections are treated consecutively with 1:50 rabbit anti-CEA serum and peroxidase-labelled swine anti-rabbit IgG. Thorough washing with TRIS (trimethamole) and saline buffer pH 7·6 is carried out between the various stages. The peroxidase activity is developed with 3, 3' diaminobenzidine tetrahydrochloride and the sections counterstained with celestine blue and mounted in Diatex.

Control sections of colon and breast carcinoma that were positive for CEA gave negative results when normal swine serum was substituted for rabbit anti-CEA serum and when this rabbit anti-CEA serum was absorbed with 1:50 solution of CEA in 0·05 M sodium phosphate buffer pH 7·5 (kindly supplied by Dr G T Rogers of the medical oncology department, Charing Cross Hospital). A different study showed that the same anti-CEA serum stained lipofuscin in normal human liver; the staining was abolished by absorbing the

TABLE I—*Details of all 69 patients studied, according to absence or presence of CEA*

Results of CEA staining	No (%) of patients	Mean age (years)	Histological type				No (%) surviving		No (%) with metastases at mastectomy
			Infiltrating duct	Lobular invasive	Tubular	Medullary	Five years	10 years	
Negative	14 (20)	54·1	9	1	3	1	13/14 (93)****	4/6 (67)***	2/14 (14)**
Positive	55 (80)	56·2	41	8	6		16/55 (29)****	4/34 (12)***	24/55 (44)**
+ +	26	55·8	18	4	4		4/26 (15)**	1/13 (8)*	10/26 (38)
+	29	56·6	23	4	2		12/29 (41)**	3/17 (18)*	14/29 (48)
Total	69 (100)	55·8	50	9	9	1	29/69 (42)	8/40 (20)	26/69 (38)

Significance of difference: *P<0·5; **P<0·05; ***P<0·01; ****P<0·001.

anti-CEA serum with normal human liver powder, but this procedure did not abolish the positive results obtained when samples of breast cancer were stained. All the sera were obtained from Dakopatts A/C (Denmark).

The statistical significance of the results was assessed by the fourfold tables of the χ^2 test. Probabilities were calculated with one degree of freedom.

Results

The mean age of the 69 patients was 55·8 years with a range of 23-79 years. Fifty tumours (72·5%) were of the infiltrating duct type, nine (13%) lobular invasive carcinoma, nine (13%) tubular, and one (1·5%) a medullary carcinoma. Twenty-four patients had lymph-node and two distal metastases (38%) (see table I). The number of affected lymph nodes, when known, varied between one and six. Mastectomy had been performed in all patients at least five years previously, and in 40 cases (58%) more than 10 years previously. Fifty-five patients (80%) were treated by mastectomy followed by radiotherapy, nine by mastectomy and radiotherapy followed by adjuvant drug treatment, and the remaining five by mastectomy alone.

The results of CEA staining were expressed in three grades—namely, negative (−), positive (+), and strongly positive (++)—according to the absence or presence of stain deposits in the tumour cells and the intensity of the staining when produced. No attempt was made to count the percentage of positive cells as most tumour cells were stainable in all positive cases. Eighty per cent of all the tumours were CEA-positive (where positive here refers to all cases that were classified as + or ++). The five- and 10-year survival rates were respectively 29% and 12% for CEA-positive tumours and 93% and 67% for CEA-negative tumours (table I). When the patients with lymph-node or distal metastases were excluded the five- and 10-year survival rates were 32% and 9% for CEA-positive tumours and 92% and 80% for the negative cases (table II). In the 50 patients with infiltrating duct carcinomas the figures were 29% and 13% for CEA-positive and 100% and 50% for CEA-negative tumours (table III). In the 26 patients with infiltrating duct carcinoma without metastases the figures were 42% and 8% for CEA-positive tumours and 100% and 67% for the CEA-negative tumours (table IV). In the 55 patients who were treated by mastectomy followed by radiotherapy the five- and 10-year survival rates were 27% and 8% for CEA-positive and 93% and 67% for CEA-negative tumours (table V).

The differences in the five-year survival rates were highly significant between patients with CEA-positive tumours and those with CEA-negative ones. For the 10-year survival the differences showed variable degrees of significance (see tables). When all patients with CEA-positive tumours were divided into two groups according to the intensity of the staining produced (+ and ++), a significant difference was observed between the five-year survival rates in the two groups ($P < 0·05$) but the corresponding figures for the 10-year survival were not significant ($P < 0·5$; table I). A significant difference in the incidence of lymph-node metastases at mastectomy was also found between patients with CEA-positive and negative tumours ($P < 0·05$).

TABLE II—*Proportions of patients without lymph-node or distal metastases at mastectomy surviving five and 10 years, according to absence or presence of CEA*

Results of CEA staining	No (%) surviving	
	Five years	Ten years
Negative	11/12 (92)*	4/5 (80)*
Positive	10/31 (32)*	2/23 (9)*
++	3/16 (19)	1/12 (8)
+	7/15 (47)	1/11 (9)
Total	21/43 (49)	6/28 (21)

*P<0·001.

TABLE III—*Proportions of patients with infiltrating duct carcinoma surviving five and 10 years according to absence or presence of CEA*

Results of CEA staining	No (%) surviving	
	Five years	Ten years
Negative	9/9 (100)**	2/4 (50)*
Positive	12/41 (29)**	3/23 (13)*
++	2/18 (11)	0/10
+	10/23 (43)	3/13 (23)
Total	21/50 (42)	5/27 (19)

*P<0·1. **P<0·001.

TABLE IV—*Proportions of patients with infiltrating duct carcinoma and no metastases at mastectomy surviving five and 10 years according to absence or presence of CEA*

Results of CEA staining	No (%) surviving	
	Five years	Ten years
Negative	7/7 (100)**	2/3 (67)*
Positive	8/19 (42)**	1/13 (8)*
++	1/8 (13)	0/5
+	7/11 (64)	1/8 (13)
Total	15/26 (58)	3/16 (19)

*P<0·02. **P<0·01.

TABLE V—*Proportions of patients treated by mastectomy followed by radiotherapy who survived five and 10 years according to absence or presence of CEA*

Results of CEA staining	No (%) surviving	
	Five years	Ten years
Negative	13/14 (93)*	4/6 (67)*
Positive	11/41 (27)*	2/24 (8)*
++	2/20 (10)	0/11
+	9/21 (43)	2/13 (15)
Total	24/55 (44)	6/30 (20)

*P<0·001.

Discussion

Three conclusions may be drawn from these results. Firstly, a relation exists between the presence of CEA in histological sections of breast carcinoma and the prognosis of the disease. The five- and 10-year survival rates are significantly better in patients with CEA-negative tumours. This relation is independent of the presence or absence of metastases, the postoperative treatment, and the histological type of the tumour. Secondly, in patients with CEA-positive tumours the prognosis worsens with the increasing intensity of the staining. Thirdly, our previously reported relation between tumour tissue containing CEA and lymph-node metastases[1] is supported by the new data.

Our results are consistent with several recent findings. CEA is one of the oncofetal antigens that are usually produced by normal fetal cells and can be produced in appreciable amounts by some malignant but not normal adult cells. The presence of such antigens is thought to be associated with behaviour common to both fetal and malignant cells, enabling them to grow rapidly, spread, and escape destruction by the response of the host tissue.[2] In colorectal carcinomas there is evidence that the preoperative serum CEA concentrations are related to the prognosis in patients with resectable tumours,[3] and the correlation between the serum CEA concentrations and the presence of lymph-node metastases approaches significance.[4] In familial medullary thyroid carcinoma the development of the invasive phase of the neoplastic process is associated with the emergence of CEA in the tumours.[5,6] In breast carcinomas the production of pregnancy proteins is associated with an increased incidence of lymph-node metastases[7] and decreased survival time.[8]

Immunoperoxidase techniques have proved their efficacy in detecting various antigens and antibodies in tissue sections, thus providing new refined cytological and histological criteria for diagnosis.[9] Our data suggest that finding CEA in tissue sections of breast carcinoma may be helpful in differentiating between tumours that appear similar by conventional histological methods yet may behave in different ways. This provides yet another

means for giving more precise prognostic information not currently available by other methods.

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Health problems of anaesthetists and their families in the West Midlands

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Summary and conclusions

A survey of all anaesthetists in the West Midlands region—that is, 10% of all the anaesthetists in England and Wales—showed that one in 10 of their children had been referred to a consultant because of a congenital or non-acquired anomaly. Abortions among anaesthetists' families were also common but more so when the mother was an anaesthetist. The anomalies were concentrated particularly in the central nervous system and musculoskeletal system, and girls were worst affected. The mean birth weights were below normal, more so when the mothers were anaesthetists. Girls with anomalies were particularly underweight. Other effects observed were unexpected infertility, cancer both in the adults and in the children, and, possibly, impaired intellectual development in the children. Many anaesthetising areas were inadequately ventilated, and scavenging devices despite their inefficiency are recommended as a stopgap measure. The results of the study closely resemble those of other studies with similar high response rates to requests for information.

Introduction

Among postulated hazards to anaesthetists are abortion,[1] underweight children,[2] congenital disorders and cancer in the children,[3] and cancer in the adults.[4] Dispute on statistical grounds[5-7] still exists despite experimental evidence that all inhalational anaesthetics are teratogenic.[8 9] Only the risk of abortion in women who work in operating departments is accepted by the DHSS.[10] Because of the disproportionate number of children of anaesthetic colleagues in Birmingham having congenital abnormalities[11] I decided to survey all anaesthetists in the West Midlands region.

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Subjects and methods

A questionnaire was sent to every anaesthetist in the region asking for details of their obstetric and relevant occupational histories for the past 20 years, their paediatric history, and whether they had had cancer. Birth weights were requested together with information on verification. An anaesthetist was defined as a doctor who spent half or more of his or her working time in anaesthetic practice. I set a limit of 20 years because (*a*) beyond that time details of obstetric history might be unreliable; (*b*) inhalational anaesthetic agents of 20 years before were still in common use; and (*c*) broadly the lifestyle of anaesthetists—their age of marriage and of starting a family—had been reasonably static during the period as compared with before, when it was common to delay establishing a family until late in their career.

The questionnaires were followed by a visit to each anaesthetic department to collect and clarify the completed returns. Any missing returns were followed up with letters, telephone calls, etc. My objective was to obtain the maximum return from the sample, which represented 10% of all anaesthetists in the United Kingdom. At each hospital visit details of the ventilation in every anaesthetising area were obtained. The anaesthetic, recovery, and operating rooms were considered as one area.

Respondents were asked not to document hernias, squints, mental health, trauma or the consequences of trauma including birth trauma, or inflammatory conditions. Diseases with an allergic basis were also excluded. The objective was to identify all non-acquired lesions. All lesions either had an anatomical basis or were diseases with an established familial background. Cases were accepted only if the child had been referred to a consultant physician or surgeon, but all referrals were accepted if the consultant established a diagnosis. Thus several conditions not normally regarded as congenital yet with a known familial background were included—for example, Henoch-Schönlein purpura, muscular dystrophy, and juvenile diabetes. Vowles *et al*[12] used the same criteria (except that hernia was not excluded) in their large survey on congenital abnormalities in the community.

I also thought that if congenital disorders were considered as being only those abnormalities that occur in the developing fetus any contribution from the fathers would be excluded (as it would be exclusive of familial disease). In view of the observations by Kripke *et al*[13] that low concentrations (20%) of nitrous oxide damage the germ cells of male animals one toxic effect of waste anaesthetics could be to induce random mutations such as occur in nature (and are responsible for the emergence of some familial diseases); alternatively by interfering with genetic make-up the dominance pattern of some recessive genes might be altered. This concept of teratogenicity is much wider than that held by Vessey,[6] who believes that a specific abnormality must be produced if an agent is a teratogen—that is, the damage must be to the fetus at a particular stage of development. To try to separate this genetic effect from any congenital effect I have classified the results according to which parent was occupationally exposed.