Estrogen receptor status of breast cancer in Ontario

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Data from a number of studies of breast cancer have suggested that after the ages associated with the menopause the rates of estrogen-receptor-positive tumours increase with age, whereas the rates of estrogen-receptor-negative tumours do not. Previous investigators studied cases in specific treatment centres, so there was a possibility that the findings were influenced by differences in patterns of case referral by age. A review of all the cases of breast cancer diagnosed in Ontario women in 1981 and assayed for estrogen receptors, however, confirmed the earlier findings. The results showed that the incidence of estrogen-receptor-positive and estrogen-receptor-negative tumours increased at about the same rate before age 45, but thereafter an increase in incidence was seen only for estrogen-receptor-positive tumours. These differences in patterns of incidence suggest the possibility that the two types of tumour may have different etiologic factors.

Certains travaux sur le cancer du sein donnent à penser qu'après les âges associés à la ménopause les taux des tumeurs porteuses de récepteurs des oestrogènes augmentent avec l'âge, au contraire des taux des tumeurs dépourvues de ces récepteurs. Jusqu'à maintenant on avait examiné des malades se présentant à des centres de traitement donnés; il restait donc possible que les résultats fussent influencés par des inégalités dans le recrutement des malades selon l'âge. Cependant la revue de tous les cas de cancer du sein reconnu chez des Ontariennes en 1981 dans lesquels on avait recherché les récepteurs des oestrogènes confirme la différence en question. Alors que l'incidence des tumeurs porteuses et dépourvues de récepteurs des oestrogènes augmente de façon presque parallèle jusqu'à l'âge de 45 ans, l'augmentation passé cet âge est notée pour les premières seules. Ces différences donnent à penser que ces deux types de tumeurs auraient des facteurs causals différents.

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In 1980 Elwood and Godolphin[1] studied over 700 cases referred to a cancer treatment centre and observed from cross-sectional data that estrogen-receptor-positive breast tumours increased in incidence with age after the menopausal ages, whereas estrogen-receptor-negative tumours did not. These observations were compatible with the findings of several smaller studies that the proportion of estrogen-receptor-positive breast tumours was higher for cases in postmenopausal than in premenopausal age groups.[2-10] The investigators had all examined data for women referred to specific institutions, so it was possible that biases in seeking care had contributed to the apparent association between the ages of the women and the estrogen receptor status of their tumours. To avoid this difficulty, we assembled information on all women who had primary malignant tumours removed from their breasts in Ontario in 1981, and we report the age-specific incidence rates in relation to the estrogen receptor status of the tumours.

Materials and methods

From the Ontario Cancer Registry we obtained data on all new cases of breast cancer diagnosed in Ontario women in 1981, from the 1981 census[11] we obtained the numbers of women in each age group resident in the province, and through the Ontario Cancer Treatment and Research Foundation we obtained laboratory reports for all the cases in which a surgical specimen of the tumour had been assayed for estrogen receptors. Using these data we calculated the age-specific incidence rates of breast cancer in Ontario women in 1981 according to the estrogen receptor status of the tumours. We were also able to assess in each age group the percentage of tumours that

← For prescribing information see page 1076

were not assayed for estrogen receptor status.

Six licensed laboratories in Ontario performed the assays, five using a dextran-coated charcoal assay and one a sucrose density gradient assay. When a tumour specimen binds at least 10 fmol of estradiol per milligram of tumour cytosol protein five of the laboratories report the estrogen receptor status as positive. One laboratory makes an exception for specimens obtained from postmenopausal women, reporting a positive status only when the amount of estradiol bound is at least 20 fmol/mg. Three laboratories report all other results as negative, but binding of less than 5 fmol/mg at two laboratories and less than 3 fmol/mg at one laboratory is reported as a negative result.

Results

A total of 3908 new cases of breast cancer in women were diagnosed in Ontario in 1981, and in 3226 cases (82.5%) specimens of the tumour were submitted for steroid receptor assay. The laboratory reports for all but 173 of the assays were sufficiently complete for use in our study: they classified the estrogen receptor status as positive, negative or intermediate and included the age of the patient. Estrogen receptor status could therefore be determined for more than 80% of tumours in women younger than 65 and about 60% of those in women older than 75 (Table I).

Among women younger than 45, the incidence rates of estrogen-receptor-positive and estrogen-receptor-negative tumours increased with age in much the same pattern (Fig. 1). Thereafter, the incidence rate of the former continued to increase with age, whereas that of the latter remained fairly constant, as did that of tumours with an intermediate estrogen receptor status.

Discussion

Our data confirm the observation in British Columbia[1] that the incidence of estrogen-receptor-positive tumours, but not estrogen-receptor-negative tumours, increases after the ages associated with the menopause. Before attempting to explain this finding we considered possible sources of bias.

Surgeons requested estrogen receptor assays in nearly 80% of the cases of primary breast cancer diagnosed in Ontario women in 1981, but the proportion was much lower for older women. To examine the possible effect of this difference we recalculated the age-specific incidence rates of estrogen-receptor-positive and estrogen-receptor-negative tumours with the extreme and unrealistic assumption that all of the tumours for which the estrogen receptor status was unavailable were neg-

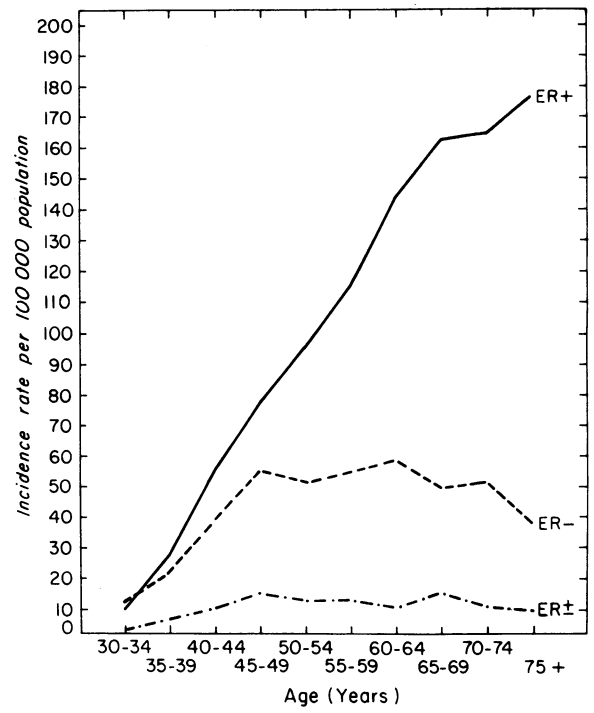

Fig. 1—Age-specific incidence rates of estrogen-receptor (ER)-positive, -negative and -intermediate tumours.

Table I—Female population at risk of breast cancer, number of cases diagnosed and percentage of tumours assayed for estrogen receptors, Ontario, 1981, as function of age

Age (yr)	Total no. of cases	Estrogen receptor status; no. of cases			% of tumours assayed	Ontario female population
		Positive	Negative	Intermediate		
30–34	90	40	38	1	88	364 390
35–39	185	76	58	15	81	289 735
40–44	262	133	80	25	91	244 725
45–49	369	177	102	36	85	231 485
50–54	416	221	105	31	86	233 405
55–59	495	267	118	31	84	233 080
60–64	455	269	99	19	85	187 710
65–69	468	266	69	26	77	164 355
70–74	373	213	58	14	76	130 270
75+	795	373	72	21	59	211 675
Total	3908	2035	799	219	78	2 290 830

ative. The patterns of incidence (available from us on request) were relatively unchanged except for the oldest group of women, in which 41% of the tumours had not been assayed for estrogen receptors; in this group the rates of estrogen-receptor-positive and estrogen-receptor-negative tumours were similar. Thus, the absence of information on estrogen receptor status for some 20% of incident cases cannot account for the shape of the incidence curves.

Although previous studies of interlaboratory quality control had shown good agreement between five of the six laboratories included in our study,[12] we examined the possibility that interlaboratory differences may have influenced the shape of the incidence curves. We found similar age distributions of cases among the laboratories, and data for five of the laboratories (available from us on request) showed that the specimens from older women were more likely than those from younger women to be estrogen receptor positive. The assays performed at the remaining laboratory were too few (40, or 1.3% of all assays) for us to draw reliable conclusions about them. It therefore seems unlikely that the incidence curves of estrogen-receptor-positive and estrogen-receptor-negative tumours were influenced appreciably by interlaboratory differences.

Another possible explanation for the variation in estrogen receptor status with age is the presence of age-related changes in hormonal levels. Premenopausal women have higher levels of endogenous estrogen; they may, therefore, have fewer unbound cytosol receptors available to be detected by the estrogen receptor assay because the receptors may have been saturated or translocated to the nucleus, or both. High levels of estrogen in the serum have occasionally been reported to accompany low levels of estrogen binding in the tumour,[13,14] but most investigators have reported no relation between levels of estrogen in serum or cytosol and tumour receptor values.[15-22] Indeed, some studies have reported higher serum levels of estradiol in patients with estrogen-receptor-positive than in patients with estrogen-receptor-negative tumours,[16-18] and one investigation revealed similar numbers of bound receptors in premenopausal and postmenopausal women, a finding that suggests that differences in unbound receptors detected by the assay cannot be explained by differences in filled receptor sites.[23] Taken together, the evidence suggests that the age-specific incidence curves for estrogen-receptor-positive and estrogen-receptor-negative tumours cannot be explained merely by hormonal changes with age.

Elwood and Godolphin[1] noted that the age-specific incidence curve for estrogen-receptor-negative tumours resembled that for breast cancer in countries with low incidence rates of the disease, such as Japan, and that the curve for estrogen-receptor-positive tumours resembled that of breast cancer in high-risk countries, such as the United States. Thus, they speculated that estrogen-receptor-positive and estrogen-receptor-negative tumours have different risk factors. Although some researchers have argued that differences in incidence rates between countries result from cohort effects,[24] such effects cannot explain our observations on estrogen-receptor-positive and estrogen-receptor-negative tumours unless two subcohorts of women in Canada are being subjected to different risk factors — that is, unless the two types of tumour have different risk factors.

Several studies have explored the possibility that traditional risk factors for breast cancer are linked with estrogen receptor status. The results have been mixed. Hildreth and colleagues[25] reported significant effects of nulliparity, age at first birth, history of breast feeding and history of benign breast disease on the estrogen receptor status of postmenopausal women; Nomura and associates[26] confirmed that the receptor status of the tumour was related to nulliparity and age at first birth but did not confirm the other findings. Three other studies failed to find significant links between tumour receptor status and nulliparity, age at first birth, family history of breast cancer or ages at menarche and menopause.[1,27,28]

Diet may play a role, as studies have detected significant associations between obesity or weight and the occurrence of an estrogen-receptor-positive tumour.[27,29,30] Other studies found similar but not statistically significant trends.[1,31] However, these findings have not always been confirmed.[25,32] In research with an experimental animal model, rats fed diets high in fat had higher levels of estrogen binding in their tumours than did those on low-fat diets.[33]

As no studies have yet been reported that examined directly the relation between diet and estrogen receptor status in human breast cancer, some of the members of our group are now conducting a study to assess possible associations.

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Meetings

continued from page 994

January

Jan. 11-17, 1986

Pan-Pacific Surgical Association's Biennial Congress
Honolulu, Hawaii
Dr. George Bondar, Secretary, Rm. 402, 10053-111 St., Edmonton, Alta. T5K 2H8

Jan. 29-Feb. 3, 1986

AO/ASIF Basic and Advanced Fracture Courses
Sunnybrook Medical Centre, Toronto
Ms. Christina Woodside, Technical Manager, Synthes (Canada) Ltd., 6790A Pacific Circle, Mississauga, Ont. L5T 1N8; 1-800-268-4733

February

Feb. 14-15, 1986

Life Style & Cardiovascular Disease 1986 Cardiac Symposium
Hyatt Regency Hotel, Vancouver
Venue West Conference Management Ltd., 750 Jervis St., Ste. 801, Vancouver, BC V6E 2A9; (604) 681-5226

March

Mar. 8-16, 1986

Advances in Oncology
Grand Hotel Savoia, Cortina d'Ampezzo, Italy
Mrs. Flavia St. Clair, Secretary, Society of Gynecologic Oncologists of Canada, Wellesley Hospital, Jones Bldg., 160 Wellesley St. E, Toronto, Ont. M4Y 1J3; (416) 926-7714

continued on page 1006