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Multiple Primary Cancers of the Breast, Endometrium and Ovary

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Abstract—*The association between cancers of the breast, endometrium and ovary is reviewed, using mainly population-based data from the cancer registries in Denmark and Connecticut, U.S.A. Breast cancer patients had an approximately three-fold increased risk of developing a cancer in the contralateral breast. The risk of breast cancer was also elevated following cancers of the corpus uteri and ovary, with relative risk (RR) estimates of about* 1.5 *from* 1 *to* 4 *years after the diagnosis of the first primary cancer. An increased risk of cancer of the corpus uteri subsequent to breast cancer was found in Connecticut, but not in Denmark. After an ovarian cancer, the risk of cancer of the corpus uteri was also elevated (RR =* 1.6–2.3*). An increased risk of ovarian cancer was observed subsequent to breast cancer (RR =* 1.3–1.7*), whereas the ovarian cancer risk decreased with time since the diagnosis of a cancer of the corpus uteri, probably reflecting treatment involving oophorectomy.*

In 1889, Billroth (cited in [1]) reported on the phenomenon of two or more independent tumours arising in the same patient. Since then, it has been recognized that the tendency to multiple primary cancers in some individuals provides a clue to the understanding of cancer aetiology. The study of multiple primary cancers has three main purposes:

1. Identification of aetiological factors, such as environmental exposures or host susceptibility factors.
2. Evaluation of carcinogenic properties of cancer treatment, e.g. radiation and chemotherapy.
3. Identification of groups of patients in need of increased medical surveillance aimed at detecting second cancers in an early stage.

In 1932, Warren and Gates [2] defined the criteria for accepting a second cancer as a new primary:

1. Each cancer must present a definite picture of malignancy.
2. Each must be distinct.
3. The possibility that one cancer represents a metastasis from the other must be excluded.

Early studies of multiple primary cancers consisted mainly of case reports and hospital series, which gave detailed accounts of the patients according to the above mentioned criteria, but no quantitative evaluation of the risk of a subsequent cancer. The first quantitative analysis was published in 1977 by Schoenberg [3], who used modern statistical techniques on the data gathered by the Connecticut Tumor Registry from 1935 to 1964. His efforts were succeeded by the analysis of the entire data materials of the cancer registries in Denmark and Connecticut from 1935 to 1982, including approximately 710,000 persons of whom more than 28,000 remained at risk after 20 years of follow-up [4]. A similar analysis was performed on about 280,000 cancer cases recorded in the Finnish Cancer Registry from 1953 to 1979 [5].

Cancer registry data offer several advantages in comparison with hospital-based series in the study of multiple primary cancers. First of all, the number of patients is sufficiently large to provide stable risk estimates. Secondly, the study population is unselected and well defined, which means that reliable estimates can be obtained of the expected number of second cancers in the population. The disadvantage of cancer registry data is that each case is rarely evaluated with the same scrutiny as in hospital series, partly because the original case notes are not available, partly because of the number of cases. Cancer registries record information on demographic factors, such as sex and age, but other information, e.g. on treatment, is often missing or unreliable.

To test specific hypotheses, however, cancer registry data can be used as a cohort in which case-

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control studies can be conducted. Cases with a particular second primary cancer are identified from the cancer registry and controls without second primary cancers are matched to the cases. The case notes are then retrieved and abstracted for pertinent details. This approach seems ideal in combining unselected registry data and detailed hospital information. It is widely used for examining adverse effects of cancer treatment [6].

In the cohort-based analysis [2, 3] of multiple primary cancers, attention is focused on the first primary cancer. This is very useful for the establishment of overall relationships, including time sequence between the two cancers, and patient surveillance. For aetiological research, however, the case-control approach, focusing on the second primary cancer, seems appropriate, when evaluating the carcinogenic events presumed to take place in the time interval between the first and the second cancer. In this review, the second primary cancer will therefore be used as the key entry, regarding the first cancer as a 'predisposing factor'.

FEMALE BREAST CANCER

Breast cancer is the most common malignant disease among women in most parts of the world. Since the survival is relatively good, a large number of women are at risk of developing a cancer in the contralateral breast. Results from hospital as well as population-based studies indicate that women with breast cancer have an approximately threefold increased risk of developing a second breast cancer [7, 8]. The possibility that some of the second breast cancers were misclassified metastases from the first breast cancer can be minimized by applying strict histopathological rules [9] or by examining the risk by time since the first primary cancer. Excluding the first 9 years of observation, the relative risk (RR) fell to about 2.5 both in the Danish and Connecticut cancer registry material [7, 8] but was still highly significant.

Table 1 shows that the risk was higher for women who had their first breast cancer diagnosed at a young age and that it decreased gradually with age, with a remarkable similarity between the estimates from Denmark [7] and Connecticut [8]. One explanation of this finding may be that some breast cancer determinants occur early in life, e.g. menarche and child births, or indeed at birth (genetic, predisposition). The influence of such factors may still prevail after the diagnosis of the first breast cancer.

Table 1. *Relative risk (with* 95% *confidence interval) of a contralateral breast cancer by age at diagnosis of the first breast cancer in Denmark* [7] *and Connecticut, U.S.A* [8]

Age at diagnosis	Denmark	Connecticut, U.S.A.
<45 years	5.5 (5.0–6.0)	5.4 (5.0–5.9)
45–54 years	3.4 (3.1–3.7)	3.4 (3.2–3.7)
55+ years	2.1 (2.0–2.3)	2.2 (2.1–2.4)
All	2.8 (2.7–3.0)	3.0 (2.9–3.2)

Another explanation of much more concern is that radiation used in the treatment of the first breast cancer may cause the second. At present, the evidence is not clear. In Connecticut [8], irradiated breast cancer patients had higher risks of second breast cancers than non-irradiated women, but there was no trend of increasing risk with time since the irradiation. In Denmark [7], irradiated patients showed higher risk estimates than the non-irradiated after the first 15 years of observation. However, cancer registry information may not be ideal for the observation of treatment effects, because a great deal of misclassification may occur. A validity check of the Danish data revealed that while some 90% of breast cancers classified as irradiated were truly so, about 40% of those classified as non-irradiated or radiation unknown had in fact received radiotherapy. More specific studies, involving dosimetry, are needed to evaluate the role of radiotherapy. Such studies are particularly important considering the use of radiotherapy in conjunction with lumpectomy in the treatment of early breast cancers, which should become increasingly common because of screening programmes.

Several studies [5, 10–14] have found an increased risk of breast cancer following an initial endometrial cancer, the RR estimates ranging from 1.2 to 2.0. In the Danish and Connecticut material (Table 2), the risk was significantly elevated only during 1–4 years after the diagnosis of the first primary cancer and did not increase with time. This may reflect an increased medical attention, i.e. the patients had their breasts examined when they had check-ups for their endometrial cancer. In the Mayo Clinic series [12], the significant risk elevation occurred 5–9 years after the endometrial cancer. However, the authors were able to analyse the influence of parity and obesity, which are well-known risk factors for both endometrial and breast cancer [15]. It turned out that a significantly increased breast cancer risk was observed only among nulliparous and obese endometrial cancer patients, the univariate RR estimates being 1.8 and 1.6 respectively, whereas the risk was not elevated among parous (RR = 1.0) and non-obese patients (RR = 1.0). This finding supports that the relationship between endometrial and subsequent breast cancer is due to common aetiological factors rather than to the endometrial cancer *per se*.

An increased breast cancer risk subsequent to ovarian cancer has appeared in several reports [11, 16–18]. Only one of these [18] examined the time sequence between the occurrence of the two

Table 2. Relative risk of breast cancer subsequent to cancers of the corpus uteri and ovary in Denmark [13] *and Connecticut, U.S.A.* [14]

Years since the first primary cancer	First primary cancer: Corpus uteri Denmark*	Corpus uteri Connecticut†	Ovary Denmark	Ovary Connecticut
<1 year	1.0	0.8	0.8	1.5
1–4 years	1.4‡	1.5‡	1.5‡	1.9‡
5–9 years	1.2	1.2	1.3	1.2
10+ years	1.1	1.2	0.7	1.1
All	1.2	1.3‡	1.1	1.4‡

*Excluding corpus uteri, NOS.
†Including corpus uteri, NOS.
‡$P < 0.05$.

cancers. As with endometrial cancer, the breast cancer risk was significantly elevated only 1–4 years after the diagnosis of ovarian cancer in Denmark and Connecticut (Table 2). Again, the role of increased medical attention cannot be ruled out. However, two opposing factors may operate in the relationship between ovarian and subsequent breast cancer. Nulliparity has been identified as a risk factor for both cancers [15], which may explain the increased breast cancer risk seen in some studies. On the other hand, the treatment of ovarian cancer involves a termination of ovarian function (surgical or by radiation), which is known to protect against breast cancer [15]. In fact, the Danish figures presented in Table 2 supports the latter, since the breast cancer risk decreased after 10 or more years of observation. In the international cohort [18], there also seemed to be a steady decline in risk after 20 years of observation, although none of the estimates differed significantly from unity, possibly because of the small number of long-term survivors.

CANCER OF THE CORPUS UTERI

Studies of cancer of the corpus uteri subsequent to a primary breast cancer have produced differing results, ranging from an excess risk [5, 8, 19] over no risk elevation [20] to a decreased risk [11]. This difference is illustrated in Table 3, where risk estimates close to unity were observed in all time periods since the breast cancer diagnosis in Denmark, while the risk of cancer of the corpus uteri was consistently elevated after the first year of observation in Connecticut. The risk estimates in Table 3 are likely to be on the low side since breast cancer patients may have had hysterectomies performed more frequently than the general population [8, 20]. The expected number of cancers of the corpus uteri would therefore be an overestimate of the true population at risk. If this was to explain the apparent discrepancy between the results, then Danish breast cancer patients should have been subjected to many more hysterectomies than the American, which seems unlikely. The possibility exists, however, that different criteria were used in Denmark and Connecticut for accepting a cancer of the uterine corpus as a new primary.

A case-control study [21] has suggested that the risk factors for endometrial cancer, such as nulliparity, late age at natural menopause and obesity, were the same among breast cancer patients and healthy women.

It is well documented [15] that oestrogens used in the treatment of menopausal symptoms increase the risk of endometrial cancer. This was also the case among breast cancer patients [21]. In one study [22] an increased risk was associated with hormones used in the treatment for breast cancer, the RR being 3.1 for hormones given during the initial course of treatment and 2.1 during a later course. However, this was not confirmed in the case-control study [21], possibly because of very few exposed individuals. Thus, an increased risk of endometrial cancer subsequent to breast cancer may be confined to the subgroup of women who possess risk factors for endometrial cancer. The strength of the association in the general population would then depend on the population level of such risk factors. Finally, no firm evidence has emerged [21] that radiation used in the breast cancer treatment affect the risk of a subsequent endometrial cancer.

Considering that the treatment of ovarian cancer frequently involves removal of the uterus, it is remarkable that an increased risk of cancer of the corpus uteri was seen subsequent to ovarian cancer [11, 13, 14]. In Connecticut (Table 3), the risk elevation was observed only within 1 year after the ovarian cancer diagnosis, which suggests that it was due to misclassified metastases. In Denmark, however, the risk stayed elevated up to 10 years after the ovarian cancer diagnosis. Since this period is probably too short for induction of an endometrial

Table 3. Relative risk cancer of the corpus uteri subsequent to cancers of the breast and ovary in Denmark [13, 20] and Connecticut, U.S.A. [8, 14]

Years since the first primary cancer	First primary cancer: Breast cancer Denmark	Breast cancer Connecticut	Ovarian cancer Denmark	Ovarian cancer Connecticut
<1 year	1.0	1.2	2.8*	2.9*
1–4 years	1.0	1.4*	2.8*	1.1
5–9 years	1.1	1.6*	3.3*	2.0
10+ years	1.0	1.3*	1.0	1.3
All	1.0	1.4*	2.3*	1.6*

*$P < 0.05$.

cancer by radiation, it is quite possible that common risk factors may be involved, of which nulliparity seems a prime candidate. Another possibility would be a persistent oestrogen secretion from the ovarian cancer.

CANCER OF THE OVARY

A positive association has been reported between breast cancer and subsequent ovarian cancer, with RR estimates ranging from 1.2 to 2.2 [5, 8, 11, 17, 19, 20]. In the Birmingham series [17], the risk was particularly high (RR = 4.4) in breast cancer patients aged less than 45 years, whereas the risk was not elevated among patients more than 60 years old. The Connecticut data [8] support this, with RR estimates of 2.6, 2.4 and 1.2 for patients aged less than 45, 45–54 and 55 years or older respectively. In Denmark (Table 4), a trend was observed of increasing ovarian cancer risk with time since the breast cancer diagnosis, while the risk remained elevated in Connecticut with no apparent trend.

The association with age and the time trend lend support to the hypothesis that common aetiologic factors are involved in breast and ovarian cancer, especially factors which operate before the menopause, e.g. child bearing and other characteristics of ovulation. However, radiation may also play a role because radiation to the ovaries has been used in the treatment of pre-menopausal breast cancer patients. Some evidence of the latter appears from the Connecticut data [8], where the risk of ovarian cancer was higher among irradiated than non-irradiated breast cancer patients. However, this was seen in practically all time periods since the breast cancer diagnosis. Since the information on radiation was non-specific, i.e. not given by site of irradiation, it must be interpreted rather cautiously.

Furthermore, two sources of error may have influenced the results presented in Table 4. First, there is the possibility of misclassified metastases from the breast cancer to the ovary. A varying tendency in Denmark and Connecticut to accept an ovarian cancer as a new primary may be the explanation to the difference in magnitude of the RR and the presence/absence of a trend. Secondly, surgical removal of the ovaries has been used as well as irradiation to terminate ovarian function mainly in pre-menopausal breast cancer patients. This would have the effect of overestimating the

Table 4. Relative risk cancer of ovarian cancer subsequent to cancers of the breast and corpus uteri in Denmark [13, 20] and Connecticut, U.S.A. [8, 14]

Years since the first primary cancer	First primary cancer: Breast cancer Denmark	Breast cancer Connecticut	Cancer of the corpus uteri Denmark*	Cancer of the corpus uteri Connecticut†
<1 year	0.9	1.8‡	2.1‡	6.4‡
1–4 years	1.2	1.4‡	1.0	0.3‡
5–9 years	1.2	1.9‡	0.7	0.7
10+ years	1.5‡	1.9‡	0.4‡	0.1‡
All	1.3‡	1.7‡	0.8	0.9

*Excluding corpus uteri, NOS.
†Including corpus uteri, NOS.
‡$P < 0.05$.

expected number of ovarian cancers, i.e. underestimating the true risk. Again, this mode of therapy may have varied in Denmark and Connecticut.

The occurrence of ovarian cancer subsequent to a cancer of the corpus uteri is difficult to interpret. Up to 80% of endometrial cancer patients have localized disease and the treatment involves removal of the ovaries. This effect is seen clearly from Table 4, where the risk of ovarian cancer decreased steadily with time since the diagnosis of endometrial cancer. The excess of ovarian cancers within 1 year of the endometrial cancer diagnosis may represent either problems in staging of the endometrial cancer, with the discovery of metastases in the ovaries after a pre-operative irradiation, or a misclassification of the endometrial cancer, in fact caused by a hormone secreting tumour of the ovary.

CONCLUSION

Studies of multiple primary cancers have found positive bidirectional associations between breast and endometrial cancer and between breast and ovarian cancer, while the association between endometrial and ovarian cancer seems more questionable. These results derive mainly from population-based cancer registries, where no information is available on risk factors and the information on treatment must be interpreted with caution.

To elucidate whether the association between breast, endometrial and ovarian cancer is due to common host factors or exposures to drugs or radiation, it is important that future studies concentrate on collection of detailed information on the following:

1. Known risk factors, such as ages at menarche and natural menopause, parity and family history.
2. Exposure to hormones prior to the development of the first primary cancer.
3. Treatment given subsequent to the first cancer. For radiation, site specific information with dosimetry should be obtained and for drugs, dose and duration of treatment periods.
4. Surgery of the uterus and ovaries to determine the true population at risk.
5. Histopathology of the two cancers to rule out that the second cancer was a metastasis of the first.

Furthermore, it is important that sufficiently large series are studied, allowing an examination of the risk by time since the first primary cancer.

Since breast cancer patients have an approximately three-fold increased risk of developing a cancer in the contralateral breast, it is advisable that screening programmes also be used to evaluate this risk. It will be particularly valuable if details are recorded on the treatment of the cancers diagnosed by screening and if follow-up is continued for women diagnosed with breast cancer to determine their risk of a contralateral breast cancer.

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