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Colorectal cancer after breast cancer: magnitude of risk in clinical practice and in the literature

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ABSTRACT

Aims and background. The aim of our study was to estimate the incidence of second primary tumors among breast cancer patients from the Division of Oncology of Andosilla Hospital (Viterbo, Italy). In particular, we studied the relationship between breast and colorectal cancer.

Methods and study design. Eligible women were those with primary invasive breast cancer who had been treated and/or followed up at our division. We compared our data with those reported in the literature.

Results. Of 114 women with breast cancer, 21 (18.5%) developed multiple primary cancers, with colorectal cancer accounting for a quarter. We found a higher incidence of colorectal cancer than reported in the literature (5% vs 0.66-1%). At the moment we are not able to explain this difference.

Conclusions. Quite a few studies reported a link between breast and colorectal cancer, but the magnitude of the risk (standardized incidence ratio 1.3-2) does not justify a screening program for colorectal disease in breast cancer patients. However, considering that the risk is small but not negligible – along with the high incidence of colorectal adenomas described in breast cancer patients and the possible existence of common risk factors – we invite clinicians not to neglect the possibility of a colorectal cancer diagnosis in women who have had breast cancer.

Introduction

Multiple primary cancers are not uncommon. A large number of studies on this issue have been published. The most important evidence from Europe and the United States showed an overall excess of 10-20% for second primary cancer¹. The risk was estimated as the observed number of second primary cancers compared with those expected from age-, sex- and registry-specific incidence rates (observed/expected standardized incidence ratio, SIR)². The correct identification of a strong site-specific association may be useful for clinicians when following up cancer patients.

In breast cancer patients, contralateral breast cancer is the most common second primary tumor. The risk ranges from 2 to 3.5 and is higher in young women (premenopausal breast cancer, SIR = 6.3)^{3,4}. These results confirm the need for a strong program of breast surveillance directed towards these patients, as recommended by international guidelines.

An excess risk of colorectal cancer following breast cancer has been reported in the literature, but its magnitude has still to be correctly quantified. However, an accurate estimation of the risk could help clinicians to establish if a woman with breast cancer must be encouraged to participate in colorectal cancer screening programs or not.

The aim of this study was to estimate the incidence of second primary tumors among breast cancer patients treated and followed up at the Division of Oncology of Andosilla Hospital (Viterbo, Italy). In particular, we studied the relationship between breast and colorectal cancer.

Key words: multiple primary cancers, breast cancer, colorectal screening, risk factors.

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Methods

We considered the total number of women with invasive breast cancer who had undergone treatment or follow-up at the Division of Oncology of Andosilla Hospital from January 2001 to May 2007. From this group we selected patients affected by multiple primary cancers. Breast cancer could be the second or first cancer site and we paid particular attention to the association between breast and colon cancer. In addition, we reviewed the most important studies evaluating multiple primary cancers and the association of breast and colorectal cancer, and compared our data with those of the literature.

Results

Of 114 women with breast cancer, 21 (18.5%) had multiple primary cancers. In Table 1 we list all cases of multiple cancer observed in the analyzed breast cancer population. The breast was the most frequent second primary cancer site: we reported 8 cases of contralateral breast cancer and 2 cases of ipsilateral breast cancer.

As regards the association between breast and colorectal cancer, we found 6 cases of colorectal cancer among the second primaries. Breast cancer was the first tumor in 5 of these 6 patients. Median age at first cancer diagnosis was 61 years (range, 48-72 years). The second primary tumor was diagnosed after 34.5 months of mean follow-up (range, 5-72 month); we found only 1 case of synchronous cancer (diagnosis of colon cancer within 6 months of breast cancer diagnosis). All second primaries were diagnosed within 5 years of the first cancer diagnosis (data not shown).

All second primary colorectal cancers were diagnosed at a locally advanced stage (pT4 or pT3 with invasion of pericolic fat tissue). Three patients had nodal metastasis (N1, N2). The only case of second primary breast cancer was pT2 pN0 (data not shown).

Table 1 - Multiple primary tumors in the breast cancer population of Andosilla Hospital (AUSL Viterbo) from 2001 to 2007

Site	Number
Breast	
Opposite breast	8
Ipsilateral breast	2
Colorectal	6
Kidney	1
Pancreas	1
Vulva	1
Ovary	1
Gastrointestinal stromal tumor (GIST)	1
All multiple sites	21
Total of breast cancer patients	114

Discussion

People with a personal history of cancer are at increased risk of subsequent primary cancer (Table 2)^{1-3,5-8}. As reported in the literature, the risk of second primary tumors in the overall cancer population ranges from 1.14 to 2.4 and is higher in young women (SIR = 4.5)^{2,4}. Some studies described an excess of several carcinomas after a diagnosis of breast cancer, with contralateral breast cancer being the most common second primary tumor (SIR = 3.5)^{3,4}.

An association between breast and colorectal cancer has been repeatedly described², but the magnitude of the risk seems ambiguous, ranging from no risk (SIR <1) to a 2-fold risk^{1-3,5,9}. For example, with regard to the Italian

Table 2 - Risk of multiple cancers according to first tumor site as reported in the literature. Breast, colon and gynecological cancers are linked by common hormonal and dietary risk factors

Reference	First cancer site	Second primary cancer	SIR	
Crocetti ⁵	Breast	Ovarian cancer	2.4	
		Corpus uteri cancer	1.3	
		Breast cancer	2.6	
		Colorectal cancer	2.4	
		Ovarian cancer	2.8	
		Colorectal cancer	2.6	
Agarwal ³	Breast	Colorectal cancer	1.3	
		Contralateral breast cancer	2.1	
		Colon cancer	2	
McCredie ⁶	Colon	Colon-rectum	1.7	
		Breast cancer	1	
		Ovarian cancer	4	
		Corpus uteri cancer	2	
		Rectum	2	
Weinberg ⁷	Ovary (age at diagnosis <50 years)	Breast cancer	1.3	
		Ovarian cancer	2.8	
		Corpus uteri cancer	1.9	
		Thyroid cancer	2.7	
Evans ⁸	Colon-rectum (age at diagnosis <65 years)	Thyroid cancer	2.5	
		Corpus uteri cancer	1.7	
		Colorectal cancer	3.67	
Buiatti ²	Breast	Colorectal cancer	3.39	
		Cervix uteri	Colorectal cancer	<1
		Colon cancer	1.28	
		Breast cancer	1.1	
		Ovarian cancer	2.56	
Mellekjær ¹	Breast (age at diagnosis <45 years)	Thyroid cancer	2.24	
		Corpus uteri cancer	1.56	
		Cervix uteri cancer	1.61	
		Rectal cancer	1.97	
Buiatti ²	Breast	Colon cancer	1.34	
		Corpus uteri cancer	1.4	
		Contralateral breast cancer	3	
Mellekjær ¹	Breast (age at diagnosis <45 years)	Colorectal cancer	1.44	
		Corpus uteri cancer	1.4	
		Ovarian cancer	2.89	

SIR, standardized incidence ratio.

population, we considered the studies of Buiatti *et al.*² and Crocetti *et al.*⁵ on 2 large cohorts of Italian cancer patients (19,252 and 240,111 patients, respectively). In Buiatti's study, the association between rectal and breast cancer stands out (rectal cancer SIR = 1.97), whereas no such association was reported in Crocetti's analyses (SIR = 0.8).

Despite these uncertain results, several common risk factors could explain the relationship between colon and breast cancer. First, some studies reported a higher risk of developing colorectal adenomas in breast cancer patients (ranging from 1.74 to 2.48)¹⁰⁻¹⁴. Colorectal adenomas represent a risk factor for colorectal cancer. Second, dietary fat promotes tumors in many animal models. In colorectal carcinogenesis, dietary fat has been hypothesized to increase the excretion of bile acids, which can be converted to carcinogens or tumor promoters¹⁵. On the other hand, in breast cancer development, free fatty acids displace estrogen from serum albumin, making it free for uptake by their receptors; they also act on cell proliferation, enhancing the number of estrogen receptors and increasing the prostaglandin concentration, which are both involved in tissue invasion and metastases¹⁶. Finally, several authors considered young age at breast cancer diagnosis as the most important risk factor for multiple cancers. Young age at diagnosis is a common feature of cancer in individuals with a genetic predisposition (Table 3)^{1,2,4,17,18}.

Breast cancer patients have a higher risk of developing a second primary cancer in other sites. From the reviewed literature, we noted a link between breast cancer and gynecological tumors and colorectal cancer. Breast

cancer patients are at risk of gynecological cancer (SIR = 2.4 for ovarian cancer and SIR = 1.4 for endometrial cancer)^{1,2,5}. Moreover, we noted that gynecological tumors are most common after colorectal cancer (SIR 2.8)⁵. On the other hand, women with a history of endometrial or ovarian cancer are considered to be at increased risk of colorectal cancer; in this population, the National Comprehensive Cancer Network recommends a screening colonoscopy at 5-year intervals, beginning at the age of diagnosis of gynecological cancer¹⁹.

This evidence could indicate the possibility of common risk factors such as hormones, diet and genetic susceptibility. For this reason, careful surveillance should be directed towards early detection of second tumors in women with a personal history of breast, colorectal and ovarian-endometrial cancer.

In conclusion, our results confirm the findings of several cohort studies carried out in Europe and the United States indicating that breast cancer patients should be monitored carefully for the occurrence of second primary cancers. In our group of breast cancer patients, we found a higher incidence of colorectal cancer than was reported in other studies (5% *vs* 0.66-1%)^{2,5}. At the moment we are not able to explain this difference. Although some studies described a link between breast and colorectal cancer, the magnitude of the reported risk (SIR = 1.3-2) does not justify a screening program for colorectal disease in breast cancer patients^{2,3,12}. However, considering that the risk is small but not negligible – along with the high incidence of colorectal adenomas (SIR = 2.48) described in breast cancer patients and the possible existence of common risk factors – we invite clinicians not to neglect the possibility of a colorectal cancer diagnosis in breast cancer patients, especially in young women¹³. The magnitude of the risk of contralateral breast cancer (about 3.5) requires annual mammographic follow-up.

Table 3 - Relationship between age at breast cancer diagnosis and risk of second primary cancer, as reported in the literature. The risk is higher in young women (<50 years)

Reference	Geographic area (Total of analyzed breast cancer patients)	No. of observed primary cancers (%)	Patient subset	SIR
Evans ¹⁷	Southeast England (145,677)	6,516 (4.4%)	Age	1.49
			<50 years	<1
			>50 years	<1
Rubino ¹⁸	France (4,416)	193 (4.4%)	All cases	1.6
			Age	2.1
Mellemkjær ¹	Europe, Canada, Australia, Singapore (525,527)	31,399 (5.9%)	All cases	1.25
			Age	1.68
Buiatti ²	Italy (5,237)	144 (2.7%)	All cases	1.6
			Age	1.58
Soerjomataram ⁴	Netherlands (9,919)	1,298 (13%)	All cases	2.4
			Pre-menopause	4.5
			Post-menopause	2

No., number; SIR, standardized incidence ratio.

References

- Mellemkjær L, Friis S, Olsen JH, Scélo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P: Risk of second cancer among women with breast cancer. *Int J Cancer*, 118: 2285-2292, 2006.
- Buiatti E, Crocetti E, Acciai S, Gafà L, Falcini F, Milandri C, La Rosa M: Incidence of second primary cancers in three Italian population-based cancer registries. *Eur J Cancer*, 33: 1829-1834, 1997.
- Agarwal N, Ulahannan MJ, Mandile MA, Cayten CG, Pitchumoni CS: Increased risk of colorectal cancer following breast cancer. *Ann Surg*, 203: 307-310, 1986.
- Soerjomataram I, Louwman WJ, de Vries E, Lemmens VEPP, Klokman WJ, Coebergh JWW: Primary malignancy after primary breast cancer in the south of the Netherlands, 1972-2001. *Breast Cancer Res Treat*, 93: 91-95, 2005.
- Crocetti E, Buiatti E, Falini P: Multiple primary cancer incidence in Italy. *Eur J Cancer*, 37: 2449-2456, 2001.
- McCredie M, Macfarlane GJ, Bell J, Coates M: Second pri-

- mary cancer after cancers of the colon and rectum in New South Wales, Australia, 1972-1991. *Cancer Epidemiol Biomarkers Prev*, 6: 155-160, 1997.
7. Weinberg DS, Newschaffer CJ, Topham A: Risk for colorectal cancer after gynecologic cancer. *Ann Intern Med*, 131: 189-193, 1999.
 8. Evans HS, Lewis CM, Robinson D, Bell CMJ, Møller H, Hodgson SV: Incidence of multiple primary cancers in a cohort of women diagnosed with breast cancer in south-east England. *Br J Cancer*, 84: 435-440, 2001.
 9. Newschaffer CJ, Topham A, Herzberg T, Weiner A, Weinberg DS: Risk of colorectal cancer after breast cancer. *Lancet*, 357: 837-857, 2001.
 10. Ochsenkühn T, Bayerdörffer E, Meining A, Späth L, Mannes GA, Wiebecke B, Eiermann W, Sackmann M, Göke O: Increased prevalence of colorectal adenomas in women with breast cancer. *Digestion*, 72: 150-155, 2005.
 11. Murray TI, Neugut AI, Garbowski GC, Waye JD, Forde KA, Treat MR: Relationship between breast cancer and colorectal adenomatous polyps. A case-control study. *Cancer*, 69: 2232-2234, 1992.
 12. Eisen GM, Sandler RS: Are women with breast cancer more likely to develop colorectal cancer? Critical review and meta-analysis. *J Clin Gastroenterol*, 19: 57-63, 1994.
 13. Bremond A, Collet P, Lambert R, Martin JL: Breast cancer and polyps of the colon: a case-control study. *Cancer*, 54: 2568-2570, 1984.
 14. Kmet LM, Cook LS, Weiss NS, Schwartz SM, White E: Risk factors for colorectal cancer following breast cancer. *Breast Cancer Res Treat*, 79: 143-147, 2003.
 15. Willett WC: Diet and cancer. *Oncologist*, 5: 393-404, 2000.
 16. Bartsch H, Nair J, Owen RW: Dietary polyunsaturated fatty acids and cancers of breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis*, 20: 2209-2218, 1999.
 17. Evans HS, Møller H, Robinson D, Lewis CM, Bell CMJ, Hodgson SV: The risk of subsequent primary cancers after colorectal cancer in southeast England. *Gut*, 50: 647-652, 2002.
 18. Rubino C, de Vathaire F, Diallo I, Shamsaldin A, Lê MG: Increased risk of second cancers following breast cancer: role of the initial treatment. *Breast Cancer Res Treat*, 61: 183-195, 2000.
 19. National Comprehensive Cancer Network (NCCN): Clinical practice guidelines in oncology: colorectal cancer screening, version 1, 2007. Available at www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf (accessed January 26, 2009).