Adipose-Derived Stems Cells and Their Role in Human Cancer Development, Growth, Progression, and Metastasis: A Systematic Review

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Abstract

Obesity is a well recognized risk factor for several types of cancers, many of which occur solely or disproportionately in women. Adipose tissue is a rich source of adipose-derived stem cells (ASC), which have received attention for their role in cancer behavior. The purpose of this systematic review is to present the existing literature on the role of ASCs in the growth, development, progression, and metastasis of cancer, with an emphasis on malignancies that primarily affect women. To accomplish this goal, the bibliographic database PubMed was systematically searched for articles published between 2001 and 2014 that address ASCs' relationship to human cancer. Thirty-seven articles on ASCs' role in human cancer were reviewed. Literature suggests that ASCs exhibit cancer-promoting properties, influence/are influenced by the tumor microenvironment, promote angiogenesis, and may be associated with pathogenic processes through a variety of mechanisms, such as playing a role in hypoxic tumor microenvironment. ASCs appear to be important contributors to tumor behavior, but research in areas specific to women's cancers, specifically endometrial cancer, is scarce. Also, because obesity continues to be a major health concern, it is important to continue research in this area to improve understanding of the impact adiposity has on cancer incidence. Cancer Res; 75(7); 1161–8. ©2015 AACR.

Introduction

Obesity is reaching epidemic proportions in the United States, affecting more than one third of the population (1). It is a risk factor for cardiovascular disease, type II diabetes, as well as many different human cancers, including breast (2), colon (3), endometrial (demonstrating the most elevated risk; refs. 4–6), and other malignancies (7). Furthermore, women appear to evidence higher incidence of cancer due to obesity compared with men. According to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database, in 2007, approximately 4% of cancer cases in men and 7% of cancer cases in women were attributable to obesity (8). Existing research linking obesity and cancer risk is predominantly focused on investigating epidemiologic risk factors as well as systemic and local tissue biomarkers (5). However, in recent years, a growing body of literature has explored how obesity leads to physiologic changes of adipose tissue itself.

Adipose tissue has notable plasticity throughout life (9) and is a highly active endocrine organ (10). It contains adipocytes, connective tissue matrices, nerve tissue, stromovascular cells, and immune cells (11). Excess adiposity leads to chronic, low-grade inflammation, which, among other factors, has been implicated in cancer development (12–17). Increasing adiposity may act via the dysregulated secretion of proinflammatory cytokines, chemokines, and adipokines to contribute to the development of cancer. Specifically, these include TNFα, IL6, leptin, adiponectin, visfatin, and plasminogen activator inhibitor (PAI)-1 (18–20).

Adipose-derived stem cells (ASC) are present within the stromal vascular fraction of adipose tissue and have tremendous plasticity. They have the ability to differentiate into numerous cell lineages, including adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, and neurogenic-like cell types (9, 21–25). They have been associated with expressing/secreting multiple important growth factors, cytokines, chemokines, and inflammatory biomarkers linked to cancer development and progression, including insulin-like growth factor (IGF), hepatocyte growth factor (HGF), TGFβ1, VEGF, IL8, Bcl-2, and IL10 (26–34). In addition, cancer cells, peritumoral adipocytes, and ASCs are thought to interact with one another, leading to more aggressive tumor behavior. In 2011, Dirat and colleagues reported that peritumoral adipocytes appear to exhibit modified phenotypic and biologic characteristics as a result of invasive cancer cells. These "cancer-associated adipocytes" in turn modify cancer cell behavior (35). Finally, adipose tissue is a significant source of circulating blood estrogen, with which body mass index is positively correlated (36). Estrogen-dependent pathways, such as those utilizing estrogen receptor-alpha (ESR1), change the biology of ASCs, potentially leading to modified behavior of the tumor and surrounding tissue.
Although there is a growing body of literature exploring the role of ASCs in the development of various human cancer types, no known review exists presenting the accumulated knowledge in this field in a systematic manner. Furthermore, ASCs’ role in cancers primarily affecting women is a growing topic of interest in the research and clinical communities. Therefore, the purpose of this systematic literature review is to explore and summarize existing knowledge on the potential role of ASCs in cancer development, growth, progression, and metastasis. We place special emphasis on cancers affecting women, as malignancies such as endometrial cancer and postmenopausal breast cancer are especially sensitive to increasing adiposity.

Materials and Methods

A search of the bibliographic resource PubMed was performed in June 2014. A combination of keywords relating to ASCs used in the literature search included: adipose-derived stem cells, ASCs, ADSCs, adipose-derived stromal cells, adipose mesenchymal cells, and cancer. Additional searches were performed that included specific malignancy terms. Figure 1 illustrates our search strategy.

Inclusion criteria

Articles were included in this review if they were published between 2001 and 2014, as 2001 appeared to be the first reference to processed liposapirate (PLA) cells (37), an early term for ASCs. All studies included in this review were published in English or had an expanded abstract in English. Investigations that used mixed animal and human cells in vivo were included, for example, those using human ASCs in mice to study tumor behavior (38, 39). Special attention was given to peer-reviewed articles that explicitly addressed the relationship between human cancer development, growth, metastasis, and ASCs. In addition, while we recognize that adipose tissue comes from several different depots (such as subcutaneous and visceral), we did not restrict this review to any one particular depot due to the paucity of literature in the area.

Exclusion criteria

Exclusion criteria were as follows: the article’s primary focus was not ASCs and their relationship to cancer, exclusively used animal models, addressed malignancies restricted to men (i.e., prostate), tested drug delivery systems instead of ASC behavior in relationship to cancer, tested tissue regeneration and cell therapy, or did not indicate that main outcome measure was not tumor development, growth, progression, and metastasis.

Results and Discussion

Of 197 initially identified articles, 37 eligible articles were included in the final review based on inclusion and exclusion criteria. We divided this review into two main areas: cancer types [typically] specific to women (Table 1) and cancer types nonspecific to women, but not restricted to men (Table 2). Figure 2 summarizes the various mechanisms by which ASCs may influence tumor development, progression, growth, and metastasis. Moderation of these reactions appears to be driven by both, positive feedback from factors such as inflammation and angiogenesis and the tumor microenvironment itself.

Complex nature of ASCs in tumor behavior

There remains controversy regarding the mechanisms by which ASCs influence tumor development, growth, progression, and metastasis; however, many of the articles identified in our review implicate ASCs in influencing tumor microenvironment. Ilmer and colleagues reported on the duality of ASCs—which they display regenerative properties but are also implicated in tumor growth and progression (40). Other authors have reported that ASCs may be protective, particularly in suppressing tumor growth and stimulating apoptosis. Most of the articles reviewed consistently pointed out that the role of ASCs in tumor development is complex, and that the tumor microenvironment milieu in which ASCs are present and the mechanisms by which they migrate may influence their role in cancer development (41–45).

Previous research has demonstrated that ASCs differentiate into various cell types such as endothelial cells, vascular complexes, and tumor stroma, facilitating tumor growth (26, 46–49). A variety of biologic pathways have been suggested regarding the ways by which ASCs are recruited. The stromal-derived factor-1/CXC receptor-4 (SDF-1/CXCR4) axis is implicated (50–52), as are various inflammation-associated chemokines and cytokines. These are released by both the tumor microenvironment and ASCs and may guide ASC migration and incorporation (47). Razmkhah and colleagues reported that ASCs express IL4, IL10, IL8, matrix metallopeptidase (MMP)-2, VEGF, and SDF-1 (27), which promoted anti-inflammatory reactions, potentially playing a crucial role in breast tumor growth and progression.
ASCs promote angiogenesis

Tumor growth and metastasis formation are dependent on the growth of blood vessels into the tumor mass, and the tumor microenvironment plays an important role in this pathologic angiogenic process (53). Adipokines secreted by ASCs have been implicated in tumor growth by promoting vascularization, a necessary component of expanding tumor mass (54). Expression of VEGF in ASCs increases in hypoxic environments, which promotes angiogenesis (55).

ASCs express growth factors that lead to increased vascularization within a variety of tumor types and pathways. Gehmert and colleagues (56) reported that ASCs may contribute to angiogenesis by migrating toward tumor-conditioned media through the platelet-derived growth factor-BB/platelet-derived growth factor receptor-B (PDGF-BB/PDGFR-B) signaling pathway. Several investigators reported on the production of VEGF by ASCs; Razmkhah and colleagues (27) reported that in ASCs, relative quantifications of VEGF were two times higher in breast cancer tissue than in controls. In addition, Zhao and colleagues (57) reported that ASCs chemoattract endothelial cells by a VEGF-dependent method. Jeon and colleagues (58) showed that the lysophosphatidic acid (LPA)–LPA1 signaling pathway played a key role in ASC differentiation and VEGF-mediated angiogenesis. Akimoto and colleagues (59) illustrated that ASCs may support glioblastoma multiforme by promoting angiogenesis, and Klopp and colleagues (60) suggested that through expressing various, specific factors, omental ASCs increase tumor vascularization in endometrial cancer.

ASCs differentiate into carcinoma-associated fibroblasts

Differentiation of ASCs to carcinoma-associated fibroblasts has been reported by a number of investigative teams. In breast cancer tumor models, Chandler and colleagues (48), Cho and colleagues (61), and Jotzu and colleagues (62) found that ASCs, when induced by factors within the tumor microenvironment, may differentiate into fibroblasts and promote tumor proliferation. Similarly, Cho and colleagues (63) and Jeon and colleagues (64) demonstrated a similar phenomenon in ovarian cancer. Do and colleagues (65) and Park and colleagues (66) illustrated this concept in lung cancer progression.

ASCs influence the tumor microenvironment

Several mechanisms linking ASCs and tumor development/progression have been described, with many studies highlighting the importance of tumor environment modification by ASCs (41–44). ASCs may play a role in the creation of an inflammatory tumor microenvironment, which promotes tumorigenic activity. Eterno and colleagues (44) suggested that ASCs may worsen tumorigenic behavior of c-Met producing breast cancer cells by creating a tumor microenvironment characterized by inflammation. The TGFβ1 signaling pathway may also play a role in the way ASCs interact with the tumor microenvironment (41). In addition, as tumor microenvironment is often hypoxic, we hypothesized that there should be a body of publications describing interconnections between ASCs and hypoxia; however, we found little mention of this research area within the existing literature.

ASCs may be associated with hypoxic tumor microenvironments

Tumor hypoxia appears to be strongly associated with tumor propagation, malignant progression, and resistance to therapy,
playing an important role in tumor physiology and cancer treatment (67). Previous research in the area of ASCs demonstrated that growth conditions utilizing a xeno-free and hypoxic environment provide an improved environment for the expansion of these cells (68). Animal studies suggested that adipose tissue is hypoxic and that local adipose tissue hypoxia dysregulates the production of adipocytokines (69). Human studies have also shown that adipose tissue is hypoxic; obesity results in reduced adipose tissue oxygenation, which is evidence for rarefaction, macrophage chemotaxis, and inflammation with an angiogenic

<table>
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<th>Proposed mechanism</th>
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<tr>
<td>Klopp et al. (60)</td>
<td>Endometrial</td>
<td>Survival and proliferation</td>
<td>Through expressing specific factors, omental ASCs increase tumor vascularization.</td>
</tr>
<tr>
<td>Chandler et al. (48, 49)</td>
<td>Breast</td>
<td>Tumorigenesis</td>
<td>Factors from BC cells inhibit adipogenic differentiation and increase proliferation, proangiogenic factor section, and myofibroblastic differentiation of ASCs.</td>
</tr>
<tr>
<td>Chandler et al. (44)</td>
<td>Breast</td>
<td>Tumorigenesis</td>
<td>Factors secreted by tumor cells lead to fibronectin expression, unfolding, and stiffening by ASCs, a hallmark of BC.</td>
</tr>
<tr>
<td>Cho et al. (61)</td>
<td>Breast</td>
<td>Progression and malignancy</td>
<td>Tumor-derived exosomes induced myofibroblastic phenotype/ functionality in ASCs via the SMAD-mediating signaling pathway, leading to EMT in tumor cells by paracrine action.</td>
</tr>
<tr>
<td>Devarajan et al. (86)</td>
<td>Breast</td>
<td>Growth</td>
<td>ASCs interact with tumor microenvironment via PDGF-D and induce EMT in tumor cells by paracrine action.</td>
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<tr>
<td>Eterno et al. (44)</td>
<td>Breast</td>
<td>Growth and angiogenesis</td>
<td>ASCs may worsen tumorogenic behavior of c-Met producing BC cells, creating inflammatory tumor microenvironment.</td>
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<tr>
<td>Gehmert et al. (56)</td>
<td>Breast</td>
<td>Growth</td>
<td>PDGF-BB increases ASC migration toward tumor-conditioned media, implicating role in tumor vascularization.</td>
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<td>Jotzu (62)</td>
<td>Breast</td>
<td>Growth, invasion, metastasis</td>
<td>ASCs differentiate into carcinoma-associated fibroblasts.</td>
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<td>Kim et al. (87)</td>
<td>Breast</td>
<td>Proliferation</td>
<td>ASCs from breast and abdominal tissue are both supportive of breast cancer proliferation.</td>
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<td>Kucerova et al. (47)</td>
<td>Breast</td>
<td>Proliferation</td>
<td>ASCs secrete exosomes, chemokines, and growth factors. Synergistic action results in proliferation.</td>
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<td>Lin R et al. (88)</td>
<td>Breast</td>
<td>Migration</td>
<td>ASCs secrete exosomes, promoting BC cell line MCF7 migration. Wnt signaling pathway activated.</td>
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<tr>
<td>Muehlberg et al. (46)</td>
<td>Breast</td>
<td>Growth and metastasis</td>
<td>ASCs incorporate into tumor vessels and differentiate into endothelial cells. BC cells enhance cell-derived factor-1 from ASCs, increasing tumor cell motility, invasion, and metastasis.</td>
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<td>Orecchinio et al. (89)</td>
<td>Breast</td>
<td>Progression and metastasis</td>
<td>Endothelial cells and ASCs cooperate in driving progression and metastasis of breast cancer.</td>
</tr>
<tr>
<td>Razmkhah et al. (90)</td>
<td>Breast</td>
<td>Growth and progression</td>
<td>Bcl-2 mRNA has 5-fold more expression in ASCs of patients with cancer. Higher stages of BC associated with higher rates of ASC proliferation.</td>
</tr>
<tr>
<td>Razmkhah et al. (41)</td>
<td>Breast</td>
<td>Growth and progression</td>
<td>IL10 and TGFβ1 significantly higher mRNA expressions in ASCs in patients with BC. Promotes anti-inflammatory reaction within tumor microenvironment.</td>
</tr>
<tr>
<td>Razmkhah et al. (27)</td>
<td>Breast</td>
<td>Growth and progression</td>
<td>In ASCs, VEGF, ILB, HGF, and IGFl 2-fold higher in patients with BC patients.</td>
</tr>
<tr>
<td>Rowan et al. (39)</td>
<td>Breast</td>
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<td>Human ASCs stimulate metastasis of MDA-MB-231 breast tumor xenografts in multiple mouse organs.</td>
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<td>Senst et al. (91)</td>
<td>Breast</td>
<td>Development</td>
<td>ASCs in breast tissue migrate to proximity of tumor foci, suggesting role in BC development.</td>
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<td>Trivanovic et al. (42)</td>
<td>Breast</td>
<td>Growth/suppression</td>
<td>ASCs from various sources exhibit similar morphology and biomarker profiles, except for CD34, Cox-2, and IDO-1. Importance of tumor microenvironment for ASC fate.</td>
</tr>
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<td>Xu et al. (92)</td>
<td>Breast</td>
<td>Metastasis</td>
<td>Invasive ability of BC cells significantly increased during ASCs’ adipogenesis.</td>
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<tr>
<td>Zhao et al. (57)</td>
<td>Breast</td>
<td>Growth and invasion</td>
<td>ASCs in breast tissue promote invasion of T4-2 cells and chemotactotrophic endothelial cells via a bFGF-independent, VEGF-A-dependent manner.</td>
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<tr>
<td>Zhao et al. (93)</td>
<td>Breast</td>
<td>Growth, invasion, metastasis</td>
<td>hASCs exerted a significantly positive effect on the invasive activity of MCF-7 cells during adipogenesis.</td>
</tr>
<tr>
<td>Zimmerlin et al. (94)</td>
<td>Breast</td>
<td>Growth</td>
<td>ASCs contain adipose-associated adipin and leptin, which promote BC growth in active but not resting tumor cells.</td>
</tr>
<tr>
<td>Cho JA et al. (63)</td>
<td>Ovarian</td>
<td>Development and growth</td>
<td>Exosomes from OC cells induce myofibroblastic phenotype and functionality of ASCs.</td>
</tr>
<tr>
<td>Jeon et al. (64)</td>
<td>Ovarian</td>
<td>Differentiation</td>
<td>Cancer-secreted LPA induced ASCs to differentiation to cancer-associated fibroblasts.</td>
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<tr>
<td>Nowicka et al. (26)</td>
<td>Ovarian</td>
<td>Proliferation, migration, chemoresistance, radiation resistance</td>
<td>ASCs detected in stroma of OC murine xenografts but not in uninvolved ovaries.</td>
</tr>
</tbody>
</table>

**Abbreviations:** BC, breast cancer; OC, ovarian cancer.
investigated whether intra-abdominal visceral adipose tissue con-
tributed to obesity and changes in adiposity (80). Klopp and colleagues
(60) utilized mouse modeling to measure chronic recruitment of ASCs by
fat and tumorigenicity in vivo and tumorigenicity in vivo (79). These
findings were correlated with changes in the gene expression profile of breast
cancer cells after coculturing with ASCs, particularly in estrogen
receptor-alpha (ERα). Other published studies in the area of breast
cancer have shown that gene expression of IL-10 and TGF-
β1 in ASCs was significantly greater than in adipose tissue of normal subjects (41).

Abdominal adipose tissue may provide a significant risk factor
Both the total volume of excess adipose tissue and more
specifically, abdominal (visceral) adipose tissue, has been shown
in the current review, which was a surprising
finding because endometrial cancer is strongly associated with
obesity and changes in adiposity (80). Klopp and colleagues
investigated whether intra-abdominal visceral adipose tissue con-
tained more endometrial tumors—promoting ASCs as compared
with subcutaneous ASCs (60). Klopp and colleagues (60) utilized
mouse modeling to measure chronic recruitment of ASCs by
fat; their findings suggested that visceral fat ASCs potentially
promote more endometrial tumor growth than ASCs from sub-
cutaneous fat. Because numerous articles implicate ASCs in hor-
monally driven cancers (such as breast), our expectation is that
future studies would evaluate the link between ASCs and endo-
metrial cancer (closely linked to excess unopposed estrogen). In
addition to the well-established unopposed estrogen link, endo-
metrial cancer risk has been linked to insulin resistance/metabolic
syndrome, steroids, and inflammatory factors (81). Although all
these mechanisms were also found to be important for general
cancers, we speculate that ASCs may play an even more profound
effect in endometrial cancer and may potentially be used as an
diagnostic marker for endometrial cancer.

Conclusions
This study demonstrated that there is a wide breadth of
available literature on the relationship between ASCs and cancer
development, including mounting evidence in the areas of ASCs’ role in the growth, progression, and metastasis of various malignancies (82–84). It appears that ASCs potentially play a role in multiple processes affecting tumor microenviron-
ment; however, few articles specifically address the influ-
ence of ASCs on tumor microenvironment. For example, there are gaps in the available literature regarding potential
hypoxic mechanisms in relation to ASCs, as well as other
discussion addressing the role of ASCs in gynecologic malign-
nancies, specifically endometrial cancer. Because adipose tissue
appears to be a key to endometrial cancer development and has
not been thoroughly evaluated in patients with endometrial
cancer, future research should aim to bridge this gap and
identify potential mechanisms implicated in endometrial

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<tbody>
<tr>
<td>Zhao et al. (52)</td>
<td>Gastric</td>
<td>Growth, migration, invasion</td>
<td>ASCs promote gastric cancer progression through the SDF-1/CXCR4 axis.</td>
</tr>
<tr>
<td>Akimoto et al. (59)</td>
<td>Glioblastoma multiforme</td>
<td>Growth</td>
<td>ASCs may support glioblastoma multiforme by promoting angiogenesis and inhibiting apoptosis.</td>
</tr>
<tr>
<td>Bago et al. (43)</td>
<td>Glioma</td>
<td>Promotion/suppression</td>
<td>ASCs have both tumor promotion and killing capabilities based on different mechanisms.</td>
</tr>
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<td>Do et al. (65)</td>
<td>Lung</td>
<td>Growth and differentiation</td>
<td>Role for LPA-stimulated ADAM12 expression in tumor growth and ASC differentiation to carcinoma-associated fibroblasts.</td>
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<td>Heo et al. (95)</td>
<td>Lung</td>
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<td>Periostin secreted by ASCs related to growth of A549 xenograft tumors in tumor microenvironment.</td>
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<tr>
<td>Jeon et al. (58)</td>
<td>Lung</td>
<td>Differentiation</td>
<td>The LPA-LPA1 signaling pathway plays a key role in differentiation of ASCs to CAFs and in VEGF-mediated angiogenesis.</td>
</tr>
<tr>
<td>Park et al. (66)</td>
<td>Lung</td>
<td>Growth and progression</td>
<td>ASCs may differentiate into myofibroblasts, playing supportive role during cancer progression.</td>
</tr>
<tr>
<td>Kucerova et al. (96)</td>
<td>Melanoma</td>
<td>Growth and proliferation</td>
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</tr>
<tr>
<td>Ji et al. (57)</td>
<td>Pancreatic</td>
<td>Proliferation and invasion</td>
<td>ASCs may be involved in the proliferation of pancreatic cancer cells via the SDF-1/CXCR4 axis.</td>
</tr>
<tr>
<td>Yu et al. (50)</td>
<td>Pancreatic</td>
<td>Proliferation and invasion</td>
<td>ASCs may be involved in the proliferation of pancreatic cancer cells via the SDF-1/CXCR4 axis.</td>
</tr>
<tr>
<td>Kandil et al. (38)</td>
<td>Thyroid</td>
<td>Growth and metastasis</td>
<td>Coinjected ASCs with K1 cell line produced larger tumors than ASC or K1 alone. Evidenced gross tumor metastasis.</td>
</tr>
</tbody>
</table>

Abbreviation: CAF, cancer-associated fibroblast.
cancer development, growth, progression, and metastasis in relation to ACS (85). Future studies should also focus on better describing the differences between various depots of adipose tissue, including identifying differences in ASCs found between subcutaneous, omental, and retroperitoneal adipose tissues. An improved understanding of the underlying biologic mechanisms associated with adiposity and human malignancies, specifically among women’s cancers such as endometrial cancer, may hold a key to better preventive strategies and improved screening programs.

Disclosure of Potential Conflicts of Interest
No conflict of interest and no commercial interest reported.

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11. Frayn KN, Karpe F, Fielding BA, Macdonald IA, Coppack SW. Integrative mechanisms associated with adiposity and human malignancies. An improved understanding of the underlying biologic mechanisms associated with adiposity and human malignancies, specifically among women’s cancers such as endometrial cancer, may hold a key to better preventive strategies and improved screening programs.

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